

OECD QSAR Toolbox v.4.2

An example illustrating RAAF scenario 6 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 prediction 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;
- 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 6;
- 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.

Outlook

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Read Across Assessment Framework (RAAF)

Overview

- RAAF has been developed by ECHA as internal tool providing a framework for a consistent and structured assessment of grouping and read across approaches under REACH.
- The outcome of the assessment is a conclusion on whether the read across is scientifically acceptable or not
- The RAAF defines different scenarios for different read-across approaches
- Each scenario is associated with particular aspects (assessment elements, AEs) that are deemed crucial to the assessment
- 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

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 ≤ 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.

Outlook

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- Workflow

The Exercise

- In this exercise we will predict a *Chromosomal aberration* of 2,3,4,5-Tetrachlorophenol [CAS# 4901-51-3], which will be the “target” chemical.
- We will preliminary define the target endpoint;
- The category will be defined by DNA binding mechanism accounting for rat liver metabolism;
- The read across approach will be used for the prediction. The read-across will be based on category 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

Outlook

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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

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 displays the QSAR Toolbox software interface. The 'Input' menu is highlighted with a red box and labeled '1'. The 'CAS#' option in the 'Single Chemical' section is labeled '2'. The search dialog box is open, showing the CAS# '4901-51-3' entered in the search field, labeled '3'. The 'Search' button is labeled '4'. The search results show the chemical structure of 2,3,4,5-tetrachlorophenol, labeled '5'.

1	CAS	4901-51-3
	SMILES	<chem>Oc1cc(Cl)c(Cl)c(Cl)c1Cl</chem>
	CS Relation	High
<input checked="" type="checkbox"/>	Substance	Mono constituent
	Composition	
	Name	2,3,4,5-Tetrachlorophenol Phenol, 2,3,4,5-tetrachloro- TETRACHLOROPHENOL...

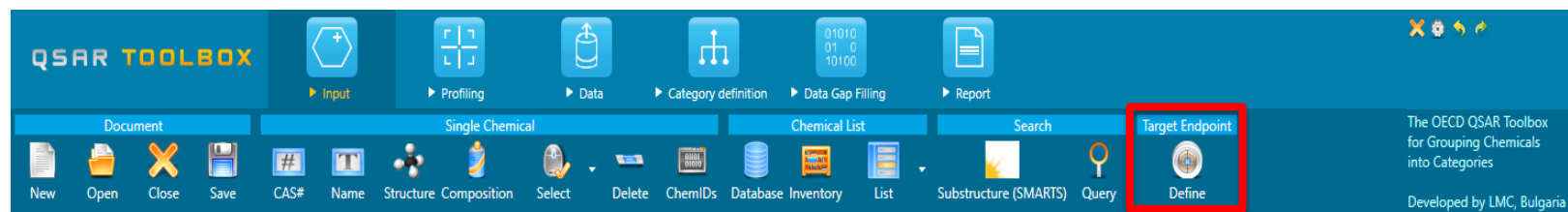
1. Go to **Input**;
2. Click **CAS#**;
3. Enter the **CAS# 4901-51-3** in the blank field;
4. Click **Search**;
5. When the structure appears click **OK**.

Input

Define target endpoint

Defining of the endpoint allows entering the endpoint of interest e.g. Chromosome aberration, EC3, LC50 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

The screenshot displays the QSAR Toolbox 4.2 interface. The top toolbar contains several icons, with the 'Define' icon (a target symbol) highlighted by a red box and labeled '1'. Below the toolbar, the 'Documents' panel shows two documents, with the second document selected and labeled '2'. The main workspace is divided into two 'Select endpoint' dialog boxes. The left dialog box shows a tree view of endpoint categories, with 'Genetic Toxicity' under 'Human Health Hazards' selected and labeled '2'. The 'Next' button at the bottom right of this dialog is labeled '3'. The right dialog box shows the configuration options for 'Genetic Toxicity', with a red box highlighting the 'Type of method', 'Test type', 'Test organisms (species)', 'Metabolic activation', 'Strain', and 'Endpoint' fields, labeled '4'. The 'Finish' button at the bottom right of this dialog is labeled '5'.

Click on **Define** (1); Expand *Human health hazards* and select **Genetic Toxicity** (2) and click **Next** (3). Select *Endpoint*: **Chromosomal aberration**, *Metabolic activation*: **With S9**, *Test organism(species)*: **Chinese hamster**, *Test type*: **In Vitro Mammalian Chromosome aberration test**, *Type of method*: **In Vitro** (4). Finally click on **Finish** (5)

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 shows the QSAR Toolbox software interface. The top menu bar includes '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 'Define' option is selected, opening the 'Filter endpoint tree...' window. This window displays a hierarchical tree of endpoints. The 'Chromosome aberration' endpoint is selected and highlighted in yellow. The corresponding row in the data matrix is also highlighted in yellow.

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 the probable mechanism(s) of action, as well as observed or simulated metabolites.

Profiling

Profiling the target chemical

1. Move to **Profiling** module
2. Tick the checkboxes of all suitable profiles and simulator (green highlighted);
3. Click **Apply**.

Profiling

Profiling results

- 1) No DNA and protein binding alerts for chromosomal aberration are identified in the target structure as a parent;
- 2) 4 metabolites are produced as a result of Rat liver S9 metabolism simulator;
- 3) General mechanistic and endpoint specific DNA binding alerts are identified in the metabolites produced by the Rat liver S9 metabolism simulator.

See on the next slide

Profiling

Profiling the target chemical

The screenshot displays the QSAR Toolbox interface for profiling a target chemical. The main window is divided into several functional areas:

- Documents:** Shows a list of documents, with the selected document having CAS: 4901513.
- Profiling methods:** A list of methods categorized into 'Suitable' and 'Plausible'. Selected methods include DNA alerts for CA and MNT by OASIS, DNA binding by OASIS, Protein binding alerts for Chromosomal aberration by OASIS, and various mutagenicity tests.
- Metabolism/Transformations:** A list of simulators. The 'Rat liver S9 metabolism simulator' is selected.
- Filter endpoint tree...:** A hierarchical tree of endpoints. The 'Chromosome aberration' endpoint is highlighted in yellow.
- Structure:** A chemical structure diagram of the target molecule.
- Results Table:** A table showing the results of the profiling. Three rows are highlighted in red and numbered 1, 2, and 3:

Endpoint	Result
Profile	No alert found
Metabolism/Transformations (Rat liver S9 metabolism simulator)	4 metabolite(s)
Endpoint Specific (DNA alerts for CA and MNT by OASIS)	1 x AN2 1 x AN2 >> Michael-type addition, quinoid structures 1 x AN2 >> Michael-type addition, quinoid structures >> Q...

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

Collecting experimental data

The screenshot shows the QSAR Toolbox interface. At the top, the 'Data' module is highlighted with a red box and a callout '1'. Below it, the 'Gather' button is highlighted with a callout '3'. In the 'Databases' section, the 'Genotoxicity OASIS' database is selected with a red circle and a callout '2'. The 'Filter endpoint tree...' window is open, showing a tree structure with 'Genetic Toxicity' expanded to 'Chromosome aberration', which is highlighted in yellow. The right side of the interface shows a chemical structure and a list of alerts.

1. Go to **Data** module;
2. Select the green highlighted *Genotoxicity OASIS* database;
3. Click **Gather**.

Data

Collecting experimental 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 database(s), which in this example is *Genotoxicity OASIS*.
- Two experimental data related to the target endpoint are found (see next slide).

Data

Collecting experimental data

The screenshot displays the QSAR Toolbox 4.2 interface. The top menu bar includes 'Data', 'Import', 'Export', and 'Delete'. The 'Data' menu is open, showing options like 'Gather', 'Import', 'IUCLID6', and 'Database Inventory'. The main window shows a 'Filter endpoint tree...' with a search filter '[target]'. A chemical structure is shown in the center. The tree lists various endpoints, with 'Chromosome aberration 1/2' highlighted in blue and circled with a red box and a callout '2'. A pop-up message box on the right says '16 points added across 1 chemicals.' with an 'OK' button and a callout '1'.

A pop-up message informs the user that there 16 experimental data found for the target chemical (1), click **OK** (1); The 2 out of 16 data points are related to the target endpoint (2);

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.
- In this case no DNA alert is identified in the target structure, but in its metabolites. Based on that the analogues will be searched accounting for rat liver metabolism. In this way the target chemical and the identified analogues will have similar metabolic pattern (see the next slides).

Category Definition

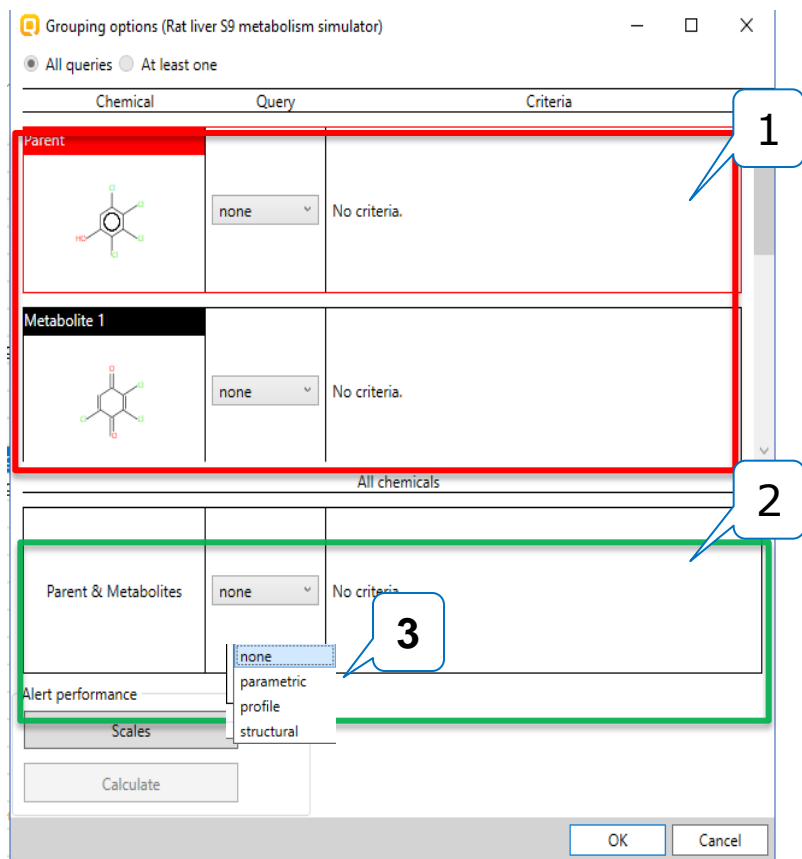
Searching for analogues accounting for *rat in vitro* metabolism

The screenshot displays the QSAR Toolbox software interface. The top toolbar has the 'Category definition' icon highlighted with a red box and labeled '1'. The left sidebar has the 'Define with metabolism' icon highlighted with a red box and labeled '2'. The central 'Filter endpoint tree' shows a tree structure with 'Rat liver S9 metabolism simulator' highlighted in yellow and labeled '3'. A 'Select metabolism' dialog box is open on the right, with 'Rat liver S9 metabolism simulator' selected and labeled '4'. The dialog box also shows other options like 'Observed Mammalian metabolism' and 'Simulated' methods.

1. Go to **Category definition** module; 2. Click **Define with metabolism**; 3. Select **Rat liver S9 metabolism simulator**; 4. Click **OK**.

Category Definition

Searching for analogues accounting for *rat in vitro* metabolism



Grouping options dialogue appears. It shows all the generated metabolites of the target chemical (use the scroll bar to see them). It has two subsections:

- (1) shows the parent and each of the generated metabolites. This allows defining different criteria for each structure when looking for analogues.
- (2) treats the parent and its metabolites as a whole. i.e. the criteria is provided for the whole package (parent & metabolites) but not for separate metabolites.

A drop down menu (3) is available in the column “Query” for each of the structures which allow setting the type of criteria for looking for analogues.

Category Definition

Searching for analogues accounting for *rat in vitro* metabolism

The screenshot displays the 'Grouping options (Rat liver S9 metabolism simulator)' window. It features a table with columns for 'Chemical', 'Query', and 'Criteria'. The 'Parent' and 'Metabolite 1' rows show chemical structures and 'none' criteria. The 'Parent & Metabolites' row has a 'profile' dropdown highlighted in red, with callout '1'. Below it, the 'Profile' dropdown is set to 'DNA alerts for CA and MNT by OASIS', with callout '2'. An 'Edit' button is highlighted with callout '3'. To the right, a 'Target' dialog box is open, showing a list of alerts. Three alerts are highlighted with red boxes and callouts: 'alert 1' (Michael-type addition, quinoid structures), 'alert 2' (DNA intercalation), and 'alert 3' (Radical mechanism via ROS formation). The 'Combine profiles' section has 'AND' selected, with callout '4' pointing to the 'OK' button.

1. Select a profile option for the package "parent & metabolites";
2. Select "DNA alerts for CA and MNT by OASIS" profile (to facilitate the search you could use the filter);
3. Click **Edit**. The profiling results of the parent and its metabolites based on DNA alerts for CA profiler;
4. Click **OK** to confirm the defined search criteria;

Category Definition

Searching for analogues accounting for *rat in vitro* metabolism

The image shows two overlapping dialog boxes from the QSAR Toolbox software. The background dialog is titled "Grouping options (Rat liver S9 metabolism simulator)". It has a table with columns "Chemical", "Query", and "Criteria". The table has two rows: "Parent" and "Metabolite 1", both with a chemical structure icon, a "none" dropdown, and "No criteria." text. Below the table is a section for "All chemicals" with a "Parent & Metabolites" dropdown set to "profile" and a "Profiler" dropdown set to "DNA alerts for CA and MNT by OAS". At the bottom left of this dialog is an "Alert performance" section with "Scales" and "Calculate" buttons, both highlighted with red boxes and callout numbers 1 and 4 respectively. The foreground dialog is titled "Aggregation options" and shows a "Categorical scale (ordinal)" dropdown set to "Maximal". Below this is a list of scales: "Chromosome aberration I (Oasis)" (highlighted with a red box and callout 2) and "Micronucleus I". At the bottom right of this dialog are "OK" and "Cancel" buttons, with the "OK" button highlighted by a red box and callout 3.

1. Click on **Scales**;
2. Select **Chromosome aberration I (Oasis)** scale;
3. Confirm by "OK";
4. Click **Calculate**.

Category Definition

Searching for analogues accounting for *rat in vitro* metabolism

Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes <AND> Nc covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes <AND> AT >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes <AND> N alert found (DNA alerts for CA and MNT by OASIS)	Positive	90.00%	Show chemicals... With data(9)...	Show all(10)...
	Negative	10.00%	Show chemicals... With data(1)...	
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	Positive	90.00%	Show chemicals... With data(9)...	Show all(10)...
	Negative	10.00%	Show chemicals... With data(1)...	
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	Positive	90.00%	Show chemicals... With data(9)...	Show all(10)...
	Negative	10.00%	Show chemicals... With data(1)...	
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	Positive	90.00%	Show chemicals... With data(9)...	Show all(10)...
	Negative	10.00%	Show chemicals... With data(1)...	
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	Positive	52.79%	Show chemicals... With data(9)...	Show all(10)...
	Negative		Show chemicals... With data(1)...	

Once the calculation of AP is finished, a new window appears providing the following information:

- 1) AP statistic accounting for all set criteria and all identified alerts in case of selected *profile* query.
- 2) AP statistic for each of the searching criteria (i.e. for each of the alerts)
- 3) Percentages of different data (positive/negative) and number of chemicals used for the statistic. The user is also able to see the corresponding chemicals (the parent chemicals are shown, only).

1 88-06-2	2 938-73-8	3 58-90-2	4 95-95-4	5 120-12-7
6 94-59-7	7 120-83-2	8 87-86-5	9 4901-51-3	

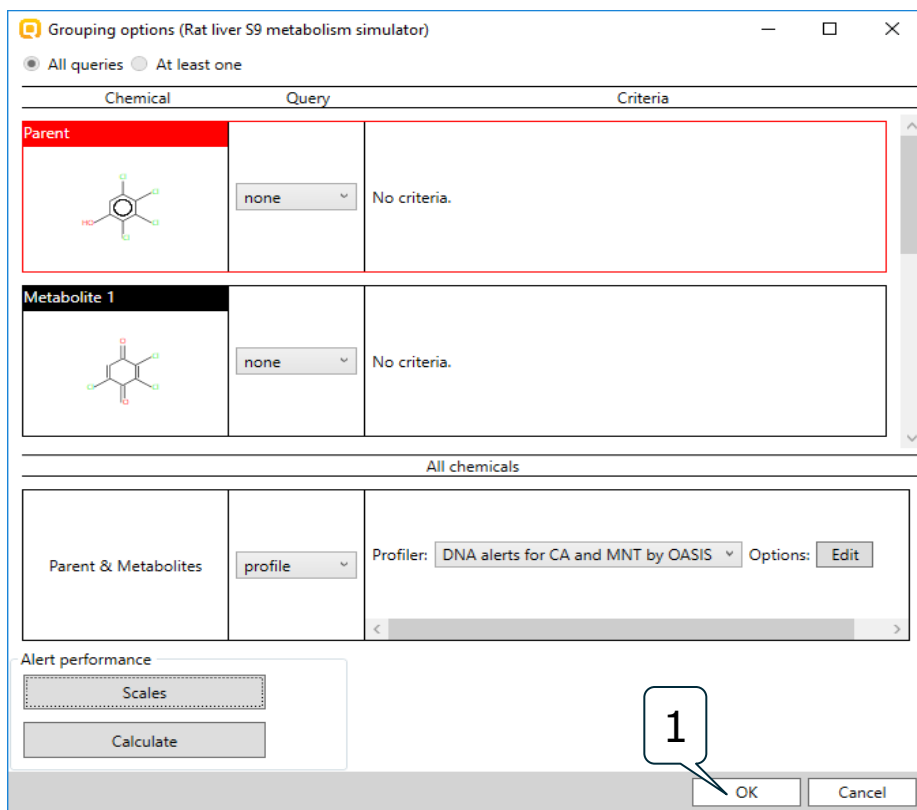
In this case calculated alert performance shows equal performance for both cases mentioned above. The performance shows that the *Quinones and Trihydroxybenzenes* alert has very high predictability with respect the defined endpoint and selected databases.

After analyzing the provided information close the window (4).

! Calculation of alert performance create a specific report item stored in the so-called *Report basket*.

Category Definition

Searching for analogues accounting for *rat in vitro* metabolism



After closing the *Alert performance* window click **OK** (1) in Grouping options window to execute the search. The Toolbox system will search within the selected database for chemicals having the same metabolic pattern with respect to *DNA alerts for CA and MNT by OASIS profiler* as the target chemical.

Category Definition

Searching for analogues accounting for *rat in vitro* metabolism

10 chemicals with 20 experimental results fulfilling the searched criteria are identified.

The screenshot shows the QSAR Toolbox interface during the 'Category definition' step. The left sidebar contains a 'Filter endpoint tree' with categories like 'Human Health Hazards', 'Genetic Toxicity', and 'Immunotoxicity'. The main workspace displays a grid of chemical structures and their corresponding experimental data. A 'Gather data' dialog box is open, indicating that 1325 points were added across 330 chemicals. A red box highlights a specific row in the data grid, which is highlighted in yellow. This row corresponds to 'Chromosome aberrations' with 10/20 M: Negative and M: Positive results.

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. Additionally, two workflows - Standardized and Automated have been developed in order to facilitate the users work. Once started, they follow the implemented logic and finish with prediction. The general differences between the two type of workflows are represented on the next slide.

In this example we will use read-across approach.

Data Gap Filling Apply Read-across

The screenshot shows the QSAR Toolbox interface. The top navigation bar contains icons for 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Workflow'. The 'Data Gap Filling' icon is highlighted with a red box and labeled '1'. In the top left corner, the 'Read across' button is highlighted with a red circle and labeled '3'. The main workspace displays a 'Filter endpoint tree' on the left and a data grid on the right. The data grid has a yellow background for the selected row. A red circle highlights a cell in the data grid containing 'M: Negative' and 'M: Positive', labeled '2'. The data grid shows various endpoints and their corresponding results for different chemical structures.

Endpoint	1 [target]	2	3	4	5	6	7	8	9	10	11	12	13
Human Health Hazards													
Acute Toxicity													
Bioaccumulation													
Carcinogenicity													
Developmental Toxicity / Teratogenicity													
Genetic Toxicity													
in Vitro													
Bacterial Reverse Mutation...	324/1190	M: Negative	M: Negative	M: Positive	M: Negative	M: Negative	M: Positive	M: Negative	M: Negative	M: Negative	M: Positive	M: Negative	M: Positive
in Vitro Mammalian Cell Micronucl...	8/8					M: Positive							
in Vitro Mammalian Chromosome Ab...													
Chinese hamster													
With S9													
Chromosome aberration	10/20	M: Negative	M: Positive			M: Positive							
Without S9	20/24	M: Negative											
Undefined Test organisms (s...	28/32						M: Positive						
Mammalian Cell Gene Mutation...	15/15						M: Positive						
in Vivo	24/36						M: Negative						
Immunotoxicity													
Irritation / Corrosion													
Neurotoxicity													
Photoinduced toxicity													
Repeated Dose Toxicity													
Sensitisation	AW SW AOP												
ToxCast													
Toxicity to Reproduction													
Toxicokinetics, Metabolism and Distribut...													
Profile													
General Mechanistic													
DNA binding by OASIS	No alert found												
Endpoint Specific	No alert found												

1. Go to **Data gap filing** module;
2. Click on the cell corresponding to target endpoint (the yellow row)
3. Click **Read-across**;

Data Gap Filling

Apply Read-across

The screenshot displays the QSAR Toolbox interface during a Data Gap Filling workflow. The main window shows a filter endpoint tree with 'Chromosome aberration' selected. A 'Choose one' dialog box is open, with 'Maximal' selected. A 'Data usage' dialog box is also open, with 'Maximal' selected. A scatter plot titled 'Read-across prediction for Chromosome aberration, based on 11 values' shows 'Chromosome aberration' on the y-axis (Positive/Negative) and 'log Kow' on the x-axis (0.5 to 5). The plot shows 11 data points, with 5 observed (blue) and 6 predicted (red/yellow). The 'Calculation options' dialog is highlighted with a red box and callout 1. The 'Data usage' dialog is highlighted with a red box and callout 2. The 'OK' button in the 'Choose one' dialog is highlighted with a blue callout 3.

1. Open **Calculation options**; 2. Select **Data usage** and choose "Maximal" (worst case scenario is applied); 3. Select **OK**.

Data Gap Filling Apply Read-across

The screenshot displays the QSAR Toolbox interface with two sub-windows, 'Sub.1' and 'Sub.2', and a main plot area. In 'Sub.1', the 'Options' list includes 'DNA alerts for CA and MNT by OASIS' and 'Rat liver S9 metabolism simulator', both highlighted with red boxes. In 'Sub.2', the 'Options' list includes 'Organic functional groups' and 'Rat liver S9 metabolism simulator', also highlighted with red boxes. The main plot area shows a 'Read-across prediction for Chromosome aberration' with a log Kow axis from 0.5 to 5.0 and a y-axis for predicted outcomes. A 'Select / filter data' panel on the right has 'Subcategorize' and 'Remove selected' buttons highlighted with red circles.

Open **Select filter data** and **Subcategorize** by 1) DNA binding alerts for CA, MN by OASIS combined with Rat liver metabolism simulator remove different 2) Organic functional groups remove different by using "Remove selected" button

Data Gap Filling

Apply Category consistency elements

After subcategorization process go back go 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*

Report Overview

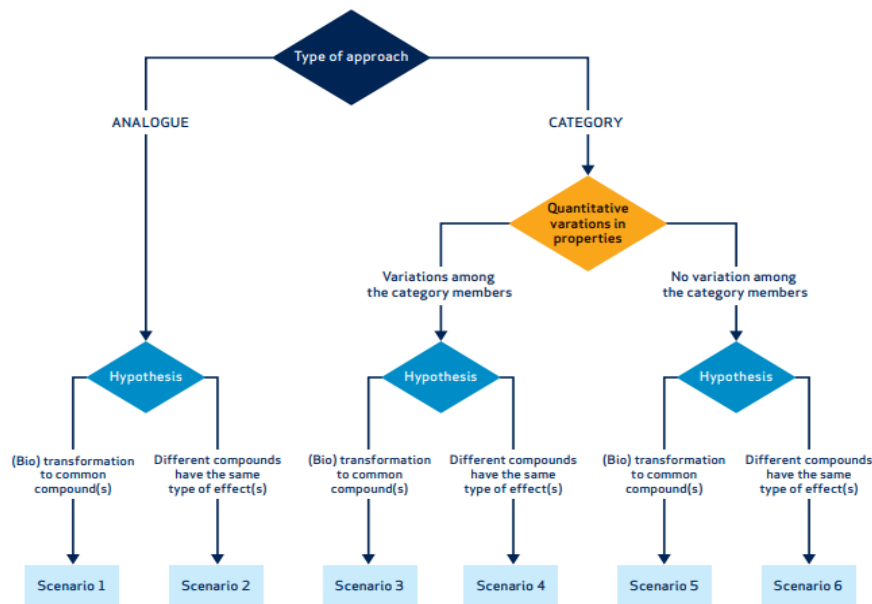
- Report module allows generating a report for any of the predictions performed within the Toolbox.
- The report module contains predefined report template which users can customize.
- Additionally specific RAAF scenario could be chosen. Selection of one of the scenarios will append automatically the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

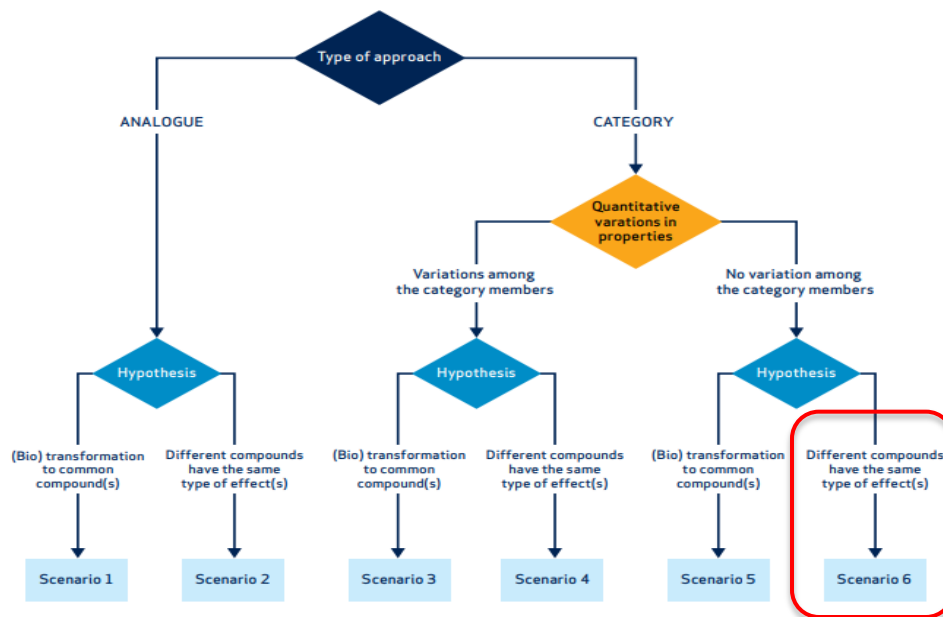
Report

Selection of RAAF scenario

For the current example:

- the type of approach applied - **category approach is used** (threshold of >3 analogues);
- the read-across hypothesis - **different compounds with common underlying mechanism**;
- For category approach - **no quantitative variations is observed among the category members**

Based on that Scenario 4 was selected for the current example.



Report

Selection of RAAF scenario

Filter endpoint tree...

Structure	1 [target]	276	277	279	282	291
Chromosome aberration 6/15	M: Negative M: Positive R: Positive	M: Positive M: Positive	M: Positive M: Positive	M: Negative M: Positive	M: Negative M: Positive	M: Negative M: Positive
Without S9 6/9	M: Negative	M: Negative	M: Positive	M: Negative	M: Negative	M: Negative
Chinese hamster Ovary (CHO) 1/2						M: Negative

US-EPA New Chemical Categories

Phenols (Acute t... Phenols (Acute t... Phenols (Acute t... Phenols (Acute t... Phenols (Acute t... Phenols (Acute t...

Read-across prediction for Chromosome aberration, based on 5 values
 Observed: Negative (x1), Positive (x1); Predicted: Positive

Chromosome aberration

Positive

Negative

2.8 3 3.2

log Kow

No quantitative variation of category members is observed with respect to target endpoint (chromosomal aberration)

Report

Report generation according to RAAF Scenario 6

The screenshot displays the QSAR Toolbox 4.2 interface. The top toolbar features a 'Report' icon (1). The left sidebar contains a 'Prediction' icon (3). The central 'Filter endpoint tree...' table shows a table of results with a cell containing 'R: Positive' highlighted in yellow (2). The 'Customize report content and appearance' wizard window is open, showing sections for 'Wizard pages' (7), 'Prediction' (4), 'Category' (5), and 'Data matrix' (6). A 'Customization' box (8) contains a checked 'Add RAAF scenario' option and a dropdown menu (9) showing 'Scenario 6' selected.

1. Go to **Report** module; 2. Select a cell with prediction – "**R: Positive**"; 3. Click **Prediction**; The **Report wizard** appears. It consists of different sections related to the types of report - **Prediction** (4), **Category** (5) and **Data matrix** (6). The content of each of these three files could be customized in the first page of the **Wizard pages** (7)
- Check the box at the top to add **RAAF scenario** (8); 4. Select **Scenario 6** from the drop-down menu (9).

Report

Report generation according to RAAF Scenario 6

AEs related to each scenario appeared automatically to the corresponding report section

The screenshot displays the 'Customize report content and appearance' interface. It is divided into three main sections:

- Left Panel (Wizard pages):** Shows navigation options. 'Target profiles' is highlighted with a red box and labeled '1'.
- Middle Panel (Customization):** Shows 'Select profiles to report' with 'AE 6.1: Compounds the test organism is exposed to' selected and highlighted with a red box and labeled '2'.
- Right Panel (Consistency check):** Shows a list of AEs related to Scenario 6, including AE 6.4, AE 6.5, AE C.3, and AE C.6, highlighted with a purple box and labeled '3'.

AEs appear in the following report sections: Target profiles (1). Category definition and members (2) and Consistency check (3).

The assessment elements of **Scenario 6** are specific distributed: one AE is included in *Target profiles* and *Category definition and members* (1, 2), and nine AEs are associated with *Consistency check* (3).

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

Report

Report generation according to RAAF Scenario 6

Section Prediction

Subsection: Target profilers

AE 6.1 Compounds the test organism is exposed to

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 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 6.1: Compounds the test organism is exposed to

Hint

PURPOSE:
In this scenario, it is claimed that different compounds have the same effects for the property under consideration. Such different compounds may be the source and target substances themselves and/or their (bio)transformation products. It has to be assessed whether:

- the compounds to which the test organism is exposed (after administration of the source and the target substances) have been established in the documentation; and
- the provided evidence supports the explanation.

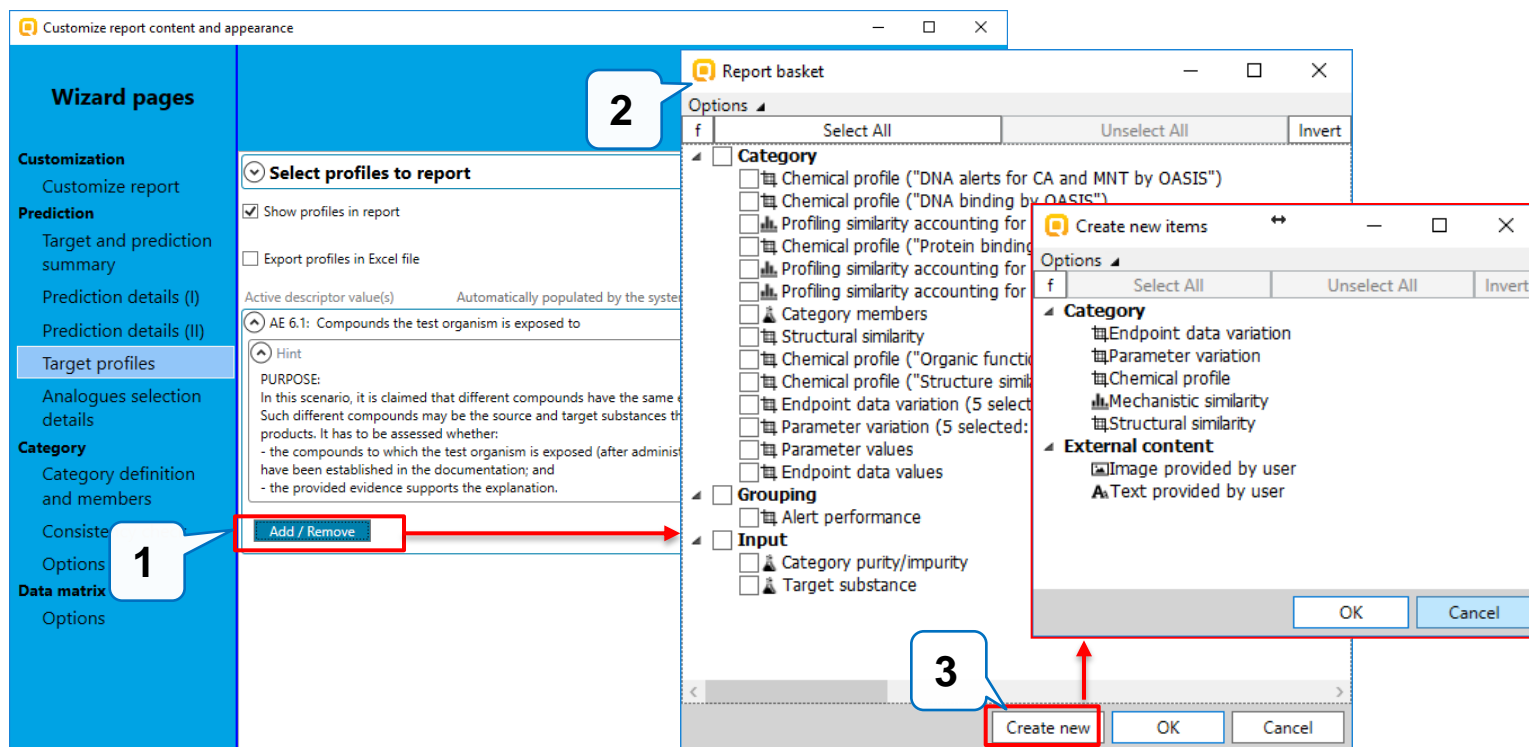
Add / Remove

Back Next Cancel Create report

1. Select **Target profiles**;
2. Expand the **AE 6.1**;
3. Hint showing the purpose of each AE is available.

Report

Report generation according to RAAF Scenario 6



Information can be included by clicking the **Add/Remove** button (1) located below the corresponding AE. The *Add/Remove* button invokes the so-called "**Report basket**" (2). 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 (3).

Items with external content (text and picture) will be added for **AE 6.1 Compounds the test organism is exposed to (see next slides)**

Report

Report generation according to RAAF Scenario 6

Section Prediction

Subsection: Target profilers

AE 6.1 Compounds the test organism is exposed to

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 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 6.1: Compounds the test organism is exposed to

Hint

PURPOSE:
 In this scenario, it is claimed that different compounds have the same effects for the property under consideration. Such different compounds may be the source and target substances themselves and/or their (bio)transformation products. It has to be assessed whether:

- the compounds to which the test organism is exposed (after administration of the source and the target substances) have been established in the documentation; and
- the provided evidence supports the explanation.

Add / Remove

Back Next Cancel Create report

The possible example text that could be added to the **AE 6.1** is:

- Five source substances (B, C, D, E and F) are used to predict the property under consideration for Target A;
- Source substances (analogues) B, C, D, E and F have common reactivity pattern;
- Functionality that may cause chromosomal aberration by three different mechanisms for DNA interaction is identified in the metabolites of all category members;
- The primary group is defined based on "Quinones and Trihydroxybenzenes" accounting for in vitro Rat metabolism.

How to add the report item with external content is illustrated on the next slide:

Report

Report generation according to RAAF Scenario 6

Section Prediction

Subsection: Target profilers

AE 6.1 Compounds the test organism is exposed to

1 Target profiles

2 Add / Remove

3 Create new

4 Text provided by user

5 OK

6 OK

7 External content

8 OK

Enter your text here:
Five source substances (B, C, D, E and F) are used to predict the property under consideration for Target A; Source substances (analogues) B, C, D, E and F have common reactivity pattern; Functionality that may cause chromosomal aberration by three different mechanisms for DNA interaction is identified in the metabolites of all category members; The primary group is defined based on "Quinone Trihydroxybenzenes" accounting for in vitro Re...ism.

Options
f Select All Unselect All

Report basket
Options
f Select All

Create new items
Options
f Select All Unselect All

Category
Endpoint data variation (5 selected: Human Health Hazards#Genetic Toxicity; Human Health Hazards#Genetic Toxicity; Human Health Hazards#Genetic Toxicity; Human Health Hazards#Genetic Toxicity; Human Health Hazards#Genetic Toxicity)

External content
Image provided by user
Text provided by user

Grouping
Alert performance
Parameter values
Endpoint data values

Input
Category purity/impurity
Target substance

External content
Text provided by user (There are target substance A and five source substances B, C, D, E and F)

Input
Category purity/impurity
Target substance

Back Next Cancel

Create new OK Cancel

Create new OK Cancel

Create new OK Cancel

In order to add text information to the report: expand the AE 6.1 (1), click **Add/Remove** (2), click **Create new** (3) in Report basket window, click **Text provided by user** (4), write in or paste the text in the appeared empty window (5), click **OK** (5) and confirm by **OK**(6). A new item called "Test provided by user.." appeared under section **External content** of the **Report basket** (7). Finally click **OK** (8).

Report

Report generation according to RAAF Scenario 6

Section Prediction

Subsection: Target profilers

AE 6.1 Compounds the test organism is exposed to

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

Select profiles to report

Show profiles in report

Export profiles in Excel file

Active descriptor value(s) Automatically populated by the system

AE 6.1: Compounds the test organism is exposed to

Hint

PURPOSE:
In this scenario, it is claimed that different compounds have the same effects for the property under consideration. Such different compounds may be the source and target substances themselves and/or their (bio)transformation products. It has to be assessed whether:

- the compounds to which the test organism is exposed (after administration and the target substances)
- the provided evidence supports the explanation.

Add / Remove

Text provided by user (Five source substances (B, C, D, E and F) are used to ...) Edit Preview

Back Next Cancel Create report

Example of how the example text will look in the generated report is shown below:

Text provided by user (Five source substances (B, C, D, E and F) are used to ...)
Five source substances (B, C, D, E and F) are used to predict the property under consideration for Target A;
Source substances (analogues) B, C, D, E and F have common reactivity pattern;
Functionality that may cause chromosomal aberration by three different mechanisms for DNA interaction is identified in the metabolites of all category members;
The primary group is defined based on "Quinones and Trihydroxybenzenes" accounting for in vitro Rat metabolism.

There are two options (2) for editing or preview the generated report item. How will look the text item in the report is shown on the right (2)

Report

Report generation according to RAAF Scenario 6

Section Prediction

Subsection: Target profilers

AE 6.1 Compounds the test organism is exposed to

Target A	Source B	Source C	Source D	Source E	Source F
EC Number:3775... 88-06-2	EC Number:3775... 87-86-5	EC Number:3774... 58-90-2	EC Number:3797... 4901-51-3	EC Number:3776... 95-95-4	EC Number:4075... 120-83-2
High	High	High	High	High	High
2,4,6Trichloroph...	2,3,4,5,6-Pentach...	2,3,4,6-Tetrachlo...	2,3,4,5-Tetrachlo...	2,4,5-Trichloroph...	2,4-Dichlorophe...

The possible image that could be added to the **AE 6.1** is:

How to add the image to the report is illustrated on the next slides:

Report

Report generation according to RAAF Scenario 6

Section Prediction

Subsection: Target profilers

AE 6.1 Compounds the test organism is exposed to

The image illustrates the process of adding a custom image to a report through three windows:

- Customize report content and appearance:** Step 1 shows the 'Add / Remove' button for the 'AE 6.1: Compounds the test organism is exposed to' section.
- Report basket:** Step 2 shows the 'Create new' button at the bottom.
- Create new items:** Step 3 shows the 'Image provided by user' option selected under 'External content'. Step 4 shows the 'OK' button.
- Select your image here:** Step 5 shows a grid of images with 'Target A' and 'Source B' through 'Source F' highlighted. Step 6 shows the 'OK' button.

In order to add picture to the report: click **Add/Remove** then click **Create new** (1) in the *Report basket* window, click **Image provided by user** (3) and then select **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). The entered picture will appear in the *Report basket* under *External content* section and the check box will be ticked. Finally confirm by **OK** (7) in the *Report basket*. As result of this a new item is added in the wizard under the AE 6.1.

*In the current example a picture illustrating the target chemical marked as **Target A** and source substances (marked with Source from B to F) was prepared in advance.

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE C.1 Substance characterization

Customize report content and appearance

Wizard pages

- Customization
 - Customize report
- Prediction
 - Target and prediction summary
 - Prediction details (I)
 - Prediction details (II)
 - Target p...
 - Analog...
 - selection details
- Category**
 - Category definition and members**
 - Consistency check
 - Options
- Data matrix
 - Options

Category definition

Category hypothesis

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 s... d be provided.

Add / Remove

Category members

Preview

Back Next Cancel Create report

Category members				
#	CAS	Name	SMILES	Structure
1	4901-51-3	2,3,4,5-Tetrachlorophenol	<chem>Oc1cc(Cl)c(Cl)c(Cl)c1Cl</chem>	
2	87-86-5	Pentachlorophenol	<chem>Oc1c(Cl)c(Cl)c(Cl)c(Cl)c1Cl</chem>	
3	58-90-2	CHLOROPHENOL, 2,3,4,6-	<chem>Oc1c(Cl)cc(Cl)c(Cl)c1Cl</chem>	
4	88-06-2	2,4,6-Trichlorophenol	<chem>Oc1c(Cl)cc(Cl)cc1Cl</chem>	
5	95-95-4	2,4,5-Trichlorophenol	<chem>Oc1cc(Cl)c(Cl)cc1Cl</chem>	

One assessment element (AE C.1) (1) related to the characterization of the category members is included in the **Category definition and members** section. It automatically populated by the system with *Category members* report item (2), which is generated during the workflow. If impurities/additives of the used analogues are available, they will be also included. The current analogues have no additives/impurities. Example on how the AE C.1. will look in the generated report is shown in right. Click on **Preview** button (3).

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.4 Exposure to other compounds than to those linked to the prediction

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 6.4: Exposure to other compounds than to those linked to the prediction

Hint

PURPOSE:
 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

Add / Remove

- AE 6.5: Occurrence of other effects than covered by the hypothesis and justification
- AE C.3: Link of structural similarity and differences with the proposed regular pattern
- AE C.6: Bias that influences the prediction

Physicochemical similarity based on calculated parameters

- Selected 2D/3D parameters for category members

Physicochemical similarity based on experimental data

- Selected physicochemical properties for category members

Comments on physicochemical similarity

Back Next Cancel Create report

The possible example text to added to the **AE 6.4** is:

- Target substance A and all source substances (B-F) do not have DNA alerts and are not responsible for the toxicity effects acting as parents.
- Alerts for DNA binding causing chromosomal aberration (Quinones and Trihydroxybenzenes alert) are identified in the metabolites of the target and the source substances after in vitro Rat liver S9 activation
- Our assumption is that the toxicity effect of the category members is caused due to formation of active metabolites rather than of the chemicals themselves.

How to add the text is shown on slide 54 :

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.4 Exposure to other compounds than to those linked to the prediction

Example on how the AE 6.4 will look in the generated report is shown :

DNA alerts for CA and MNT by OASIS	P1	P2	P3	P4	P5	P6
No alert found	2	5	5	4	4	5
Quinones and Trihydroxybenzenes	3	3	3	3	3	3

Additionally to the text, the profiling similarity accounting for metabolism could be also included. To do this click on **Add/Remove** button then check the box of **Profiling similarity (the six ordered box)**(2). The item is stored in the report basket, during the actions performed in the section Profiling. Right click and select **Preview** button(3). Tables summarizing the number of metabolite including the parent with the alerts is provided (4).

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.5 Occurrence of other effects than covered by the hypothesis and justification

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 definition and members
 - Consistency check**
 - Options
- Data matrix
 - Options

AE 6.4: Exposure to other compounds than to those linked to the prediction

AE 6.5: Occurrence of other effects than covered by the hypothesis and justification

Hint

PURPOSE:
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

Add / Remove

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

AE C.6: Bias that influences the prediction

Physicochemical similarity based on calculated parameters

Selected 2D/3D parameters for category members

Physicochemical similarity based on experimental data

Selected physicochemical properties for category members

Comments on physicochemical similarity

Structural similarity

Justification for selected structure similarity profilers

Back Next Cancel Create report

The possible example text to be added to the **AE 6.5** is:

- The target substance A and source substances B, C, D, E and F have common reactivity pattern based on presence of Quinones and Trihydroxybenzenes functionality in the structures of their metabolites;
- The Quinones and Trihydroxybenzenes functionality could cause toxicity effect by three different mechanisms for DNA binding;
- No other functionalities causing chromosomal aberration by DNA damage have been identified in the structures of the parents and metabolites.

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

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

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 definition and members
 - Consistency check**
 - Options
- Data matrix**
 - Options

AE 6.4: Exposure to other compounds than to those linked to the prediction

AE 6.5: Occurrence of other effects than covered by the hypothesis and justification

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

Physicochemical similarity based on calculated parameters

Selected 2D/3D parameters for category members

Physicochemical similarity based on experimental data

Selected physicochemical properties for category members

Comments on physicochemical similarity

Structural similarity

Back Next Cancel Create report

The possible content of text added to the **AE C.3** is:

- No alerts related to chromosomal aberration have been identified in the structures of the target and the source substances.
- Target and analogues are activated as a result of in vitro S9 metabolism simulator by generating "Quinones and Trihydroxybenzenes";
- In this respect, the structurally defined category from target (A) and five source substances (B, C, D, E, F) have common reactivity pattern of generated in vitro S9 metabolites.

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE C.6 Bias that influences the prediction

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 6.4: Exposure to other compounds than to those linked to the prediction
 AE 6.5: Occurrence of other effects than covered by the hypothesis and justification
 AE C.3: Link of structural similarity and differences with the proposed regular pattern
 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

Physicochemical similarity based on calculated parameters

Selected 2D/3D parameters for category members

Physicochemical similarity based on experimental data

Selected physicochemical properties for category members

Comments on physicochemical

Back Next Cancel Create report

The possible example text which could be added to the **AE C.6** is:

- The analogues are obtained based on a grouping accounting for in vitro rat liver metabolism;
- All analogues having different metabolic pattern with respect to DNA interaction causing chromosomal aberration have been removed during the subcategorization process.
- The identified five analogues used in the read-across prediction have the common functional groups according to the OFG profiling scheme and the same reactivity pattern with respect to DNA interaction;

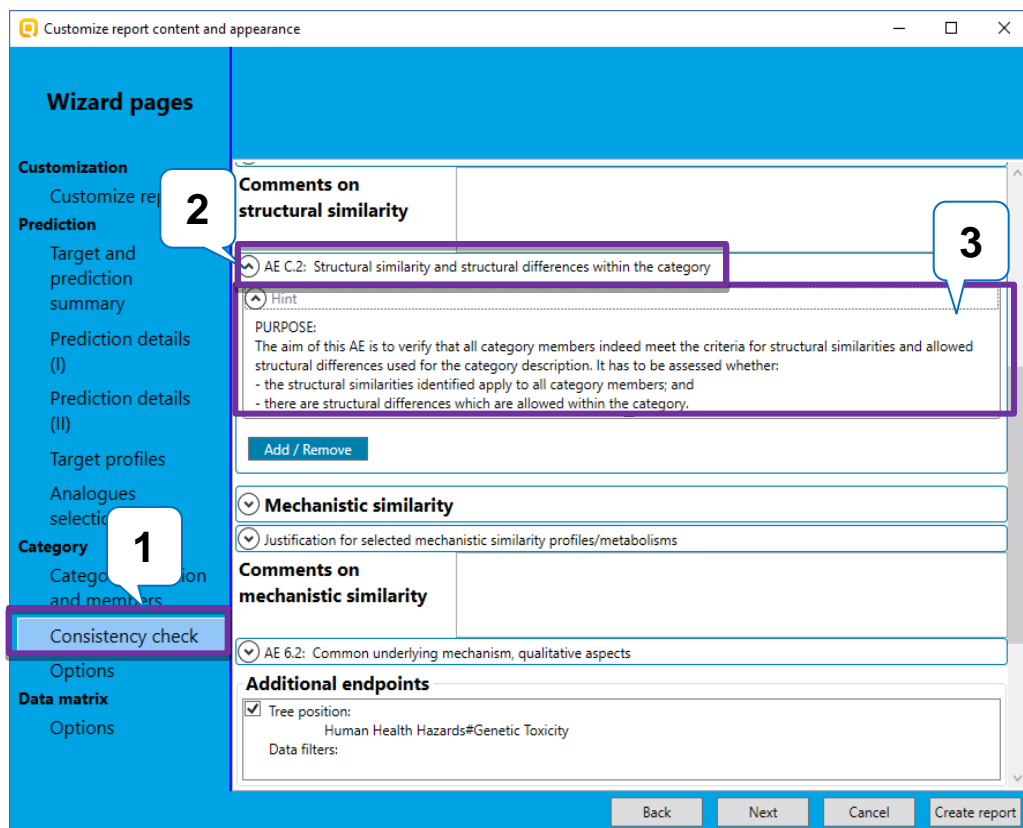
Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

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



The possible content of the text which could be added to the **AE C.2** is:

- Structural similarity between Target substance A and five source substances (B, C, D, E and F) according to Str. similarity profiler is in the range of [29 - 82%]
- Target A and substances B, C have same functionalities with respect to OFG profiler
- Source substance D, E and F have same functionalities as target A, with exception of one group: *Aromatic perhalogenocarbons*

Appendix with similarity table and profile statistics for OFG profiler could be provided here (see next two slides):

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

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

The screenshot shows the 'Customize report content and appearance' window on the left and the 'Report basket' window on the right. The 'Report basket' window displays a list of categories and their members. Callout 1 points to the 'Add / Remove' button in the 'Consistency check' section. Callout 2 points to the 'Structural similarity' item in the 'Report basket'. Callout 3 points to the 'Preview' option in the context menu for 'Structural similarity'. Callout 4 points to the 'Calculated structure similarity' table.

Example with how the AE C.2 will look in the generated report is shown below:

Structural similarity

Options

Mode: Hologram, CombineAllFeatures

Measure:

-Dice

Molecular features:

-AtomCenteredFragments

Atom characteristics:

-AtomType

-CountHAttached

-Hybridization

Calculated structure similarity

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	Chemical 5	Chemical 6
Chemical 1	100%	69.6 %	81.8 %	57.1 %	66.7 %	60 %
Chemical 2	69.6 %	100%	69.6 %	45.5 %	36.4 %	28.6 %
Chemical 3	81.8 %	69.6 %	100%	76.2 %	66.7 %	50 %
Chemical 4	57.1 %	45.5 %	76.2 %	100%	80 %	63.2 %
Chemical 5	66.7 %	36.4 %	66.7 %	80 %	100%	63.2 %
Chemical 6	60 %	28.6 %	50 %	63.2 %	63.2 %	100%

Two additional items have to be added in order to support the textual information: Click **Add/Remove** button (1) and check the **Structural similarity** item (2) which is stored in the **Report basket**. Right click and **preview** the item (3). A table providing structural similarity between each of the category members is shown (4).

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

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

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

Comments on structural similarity

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

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.

Mechanistic similarity

Justification for selected mechanistic similarity profiles/metabolisms

Comments on mechanistic similarity

AE 6.2: Common underlying mechanism, qualitative aspects

Additional endpoints

Tree position:
Human Health Hazards#Genetic Toxicity

Data filters:

Back Next Cancel Create report

The possible report item containing image file could be added to the **AE C.2** is (see slide 57 with instructions how to create it):

Appendix with profiling statistics based on OFG profiler could be added:

Profile Statistic

Group by category

#	Category	Count	%
1	Aromatic perhalogenocarbons-Aryl-Aryl halide	3	50.00
2	Aryl-Aryl halide+Phenol	3	50.00

Save to smi Print Add in new doc

1 95-95-4
2 120-83-2
3 88-06-2

Actions

Organic functional groups

Count

Aromatic perhalo... Aryl-Aryl halide...

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.2 Common underlying mechanism, qualitative aspects

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.2: Structural similarity and structural differences within the category

Mechanistic similarity

Justification for selected mechanistic similarity profiles/metabolisms

Comments on mechanistic similarity

AE 6.2: Common underlying mechanism, qualitative aspects

Hint

PURPOSE:
The hypothesis/justification has to explain how the compounds the test organism is exposed to lead to the same type of effects/absence of effects. It has to be assessed whether:

- the documentation has established a common underlying mechanism;
- this mechanism links the structures of these compounds under consideration with the possibility to predict qualitatively similar type of effects for the target substance for the property under consideration; and
- the provided evidence supports the explanation.

Add / Remove

Additional endpoints

Tree position:
Human Health Hazards#Genetic Toxicity

Data filters:

Category values for selected additional endpoints

Comments on

Back Next Cancel Create report

The possible example text for **AE 6.2** is

- Target substance A and source substances B, C, D, E and F react via a common underlying mechanism according to *DNA alerts for CA and MNT by OASIS*
- *Quinones and Trihydroxybenzenes* functionality alert is identified in all category members after metabolic activation (see Appendix Metabolite/Profiling)
- Common mechanism is illustrated in Appendix Metabolites/Profiling
- Our assumption is that the toxic effect is based on *Quinones and Trihydroxybenzenes* functionality
- As a primary group is used the *Quinones and Trihydroxybenzenes* group presented with three different mechanism of actions, supported by the calculated alert performance
- The similarity with respect to the metabolic pattern could be seen in **AE 4.5.** above.

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

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.2 Common underlying mechanism, qualitative aspects

The screenshot shows the 'Customize report content and appearance' window. On the left, the 'Wizard pages' sidebar is visible, with 'Consistency check' highlighted. The main area shows the 'Mechanistic similarity' section. A 'Report basket' dialog is open, showing a list of items to be included in the report. The 'Alert performance' item is checked, and the 'OK' button is highlighted. Numbered callouts 1-4 indicate the steps: 1. Clicking 'Consistency check' in the sidebar, 2. Clicking 'Add/Remove' for the 'Alert performance' item, 3. Checking the 'Alert performance' checkbox in the 'Report basket', and 4. Clicking the 'OK' button.

Example on how the Alert performance included in the **AE 6.2** will look in the generated report is shown:

#	Alert name	Alert performance, %		Number of chemicals	
		Positive	Negative	Positive	Negative
1	Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Quinones and Trihydroxybenzenes<-AND> Quinones and Trihydroxybenzenes<-AND> Quinones and Trihydroxybenzenes<-AND> No alert found (DNA alerts for CA and MNT by OASIS)	90.00	10.00	9	1
2	Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	90.00	10.00	9	1
3	Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	90.00	10.00	9	1
4	Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Quinones and Trihydroxybenzenes (DNA alerts for CA and MNT by OASIS)	90.00	10.00	9	1
5	Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: No alert found (DNA alerts for CA and MNT by OASIS)	52.79	47.21	104	93

AE 6.2 is related to the mechanistic similarity of the final category. All items in the report basket related to the mechanistic consistency of the category are added automatically if category consistency is applied preliminary (1). Only the Alert performance item have to be included here manually, so click on **Add/Remove** (2), then check the **Alert performance** item (3) and click **OK** (4).

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.3 Common underlying mechanism, quantitative aspects

The screenshot displays the 'Customize report content and appearance' window. On the left, the 'Wizard pages' sidebar includes 'Customization', 'Prediction', 'Category', and 'Data matrix'. The 'Consistency check' page is active. The main area shows a 'Report basket' dialog with a tree view of categories. A callout box labeled '1' points to the 'Add / Remove' button at the bottom of the 'Consistency check' page. A callout box labeled '2' points to the 'External content' checkbox in the 'Report basket' tree. A callout box labeled '3' points to the 'OK' button in the 'Report basket' dialog.

The possible text added for the **AE 6.3** is:

- Target substance A and five source substances has common reactivity pattern
- They all formed *Quinones and Trihydroxybenzenes* functionality as metabolites responsible for the toxicity effects
- Toxic effects of all source substances and target are supported by the identified additional genotoxicity data – see *Data matrix* file generated by prediction Report

Include the Endpoint data variation item stored in the report basket (1).

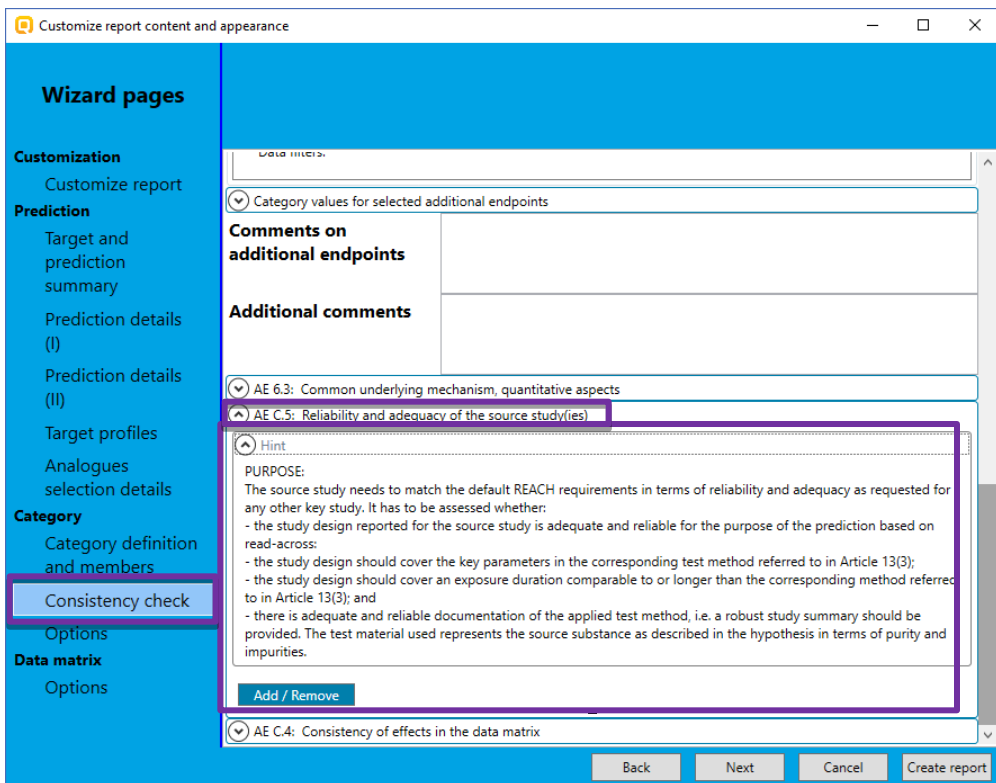
Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.5 Reliability and adequacy of the source study(ies)



The possible example text is:

- The target substance have been tested according to *in Vitro Mammalian Chromosome Aberration Test*
- All the experimental data for the five source substances has been tested based on *in Vitro Mammalian Chromosome Aberration Test* and are used for the prediction of Chromosomal aberration of the target substance A

A snapshot from *Filter points by test conditions* could be provided (see next slide).

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE 6.5 Reliability and adequacy of the source study(ies)

The possible image added to the text in AE C.5 in RAAF scenario 6:

Endpoint	276	277	279	282	291
Chromosome aberration	M: Negative R: Positive	M: Positive	M: Positive	M: Negative	M: Negative
Without 59	6/9 M: Negative	M: Negative	M: Positive	M: Negative	M: Negative
Chinese hamster Ovary (CHO)	1/2				M: Negative
Hamster	1/5				M: Negative
Undefined Test organisms (spe...)	2/5		M: Negative		M: Equivocal
Mammalian Cell Gene Mutation A...	2/7		M: Positive		M: Negative
Other	1/1				M: Positive
Sister Chromatid Exchange Assay L...	1/5				M: Positive
in Vivo	2/9	M: Inconclusive			M: Negative

Read-across prediction for Chromosome aberration, bar
Observed: Negative (x1), Positive (x1); Predicted: Post

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE C.4 Consistency of effects in the data matrix

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

additional endpoints

Additional comments

AE 4.3: Common underlying mechanism, quantitative aspects

AE C.5: Reliability and adequacy of the source study(ies)

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

Hint

PURPOSE:
The category justification should include comparison of experimental data for the category members and a clear data matrix. It has to be assessed whether:

- a data matrix has been provided which lists the category members in a suitable order versus their experimental data (e.g. for REACH information requirements) and which identifies data gaps;
- the properties of category members across the data matrix are consistent in effects; this has to be assessed in the following dimensions:
 - within the specific property which is under consideration for the prediction;
 - between the property under consideration and related properties (e.g. between 28-day and 90-day repeated-dose toxicity studies; reproductive toxicity screening tests; and pre-natal developmental toxicity studies);
 - characteristics across all relevant properties (e.g. different reactivity towards genetic material may indicate different reactivity towards biological macromolecules which may influence the prediction for a 90-day repeated-dose toxicity study);
- the effects reported for the property under consideration differ in strength for the source substance and whether a basis for this difference is provided; and
- the underlying data support the provided conclusions and explanations.

Add / Remove

Back Next Cancel Create report

The possible text to added to the **AE C.4** is:

- The target substance A and the five source substances (B, C, D, E and F) show indication for chromosomal aberration effect.
- The latter is supported by the experimental data identified for AMES mutagenicity effect (caused also by DNA damage) found for target and source substances.

Here could be provided the data matrix snapshot or reference to the *Data matrix report* (see next slide).

Report

Report generation according to RAAF Scenario 6

Section Category

Subsection: Category definition and members

AE C.4 Consistency of effects in the data matrix

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

additional endpoints

Additional comments

AE 4.3: Common underlying mechanism, quantitative aspects






AE C.5: Reliability and adequacy of the source study(ies)

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

Hint

PURPOSE:
The category justification should include comparison of experimental data matrix. It has to be assessed whether:
- a data matrix has been provided which lists the category members in a (e.g. for REACH information requirements) and which identifies data gaps
- the properties of category members across the data matrix are consistent following dimensions:
- within the specific property which is under consideration for the dose toxicity studies; reproductive toxicity screening tests; and pre-natal developmental toxicity studies);
- characteristics across all relevant properties (e.g. different reactivity towards genetic material may indicate different reactivity towards biological macromolecules which may influence the prediction for a 90-day repeated-dose toxicity study);
- the effects reported for the property under consideration differ in strength for the source substance and whether a basis for this difference is provided; and
- the underlying data support the provided conclusions and explanations.

Add / Remove

1	Target chemical	Neighbour #1	Neighbour #2	Neighbour #3	Neighbour #4	Neighbour #5	
2	Structure						
3	CAS number	4901-91-9	87-86-5	58-90-2	88-06-2	95-95-4	
4	Chemical name	2,3,4,5-Tetrachlorophenol	Pentachlorophenol	CHLOROPHENOL, 2,3,4,6-	2,4,6-Trichlorophenol	2,4,5-Trichlorophenol	
5	Other identifier						
6	SMILES	Clc1c(Cl)c(Cl)c(Cl)c1	Clc1c(Cl)c(Cl)c(Cl)c(Cl)c1	Clc1c(Cl)c(Cl)c(Cl)c1	Clc1c(Cl)c(Cl)c(Cl)c1	Clc1c(Cl)c(Cl)c(Cl)c1	
7	Parameters	unit					
10	Vapor Pressure (Antoine method)	mm Hg	0.000136	0.0000757	0.000411	0.0054	
11	Molecular Weight	Da	231.87588	266.31794	231.87588	197.43382	
12	log Pow		4.09	4.74	4.09	3.45	
13	Boiling point	°C	288.07	311.71	288.07	282.08	
14	Water Solubility	mg/L	28.69	3.09	17.9	121	
15	Profiles						
16	Profiles used for grouping/subcategorization	Parent and 4 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect), Radical >> Quinones and Trihydroxybenzenes (DNA-alerts for Ca and Mn) by (GHS) (primary group)	Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 2 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 4 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes
17		Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 4 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: ANZ, ANZ >> Michael-type addition, quinoid structures, ANZ >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	

The image added to the AE C.4:

The OECD QSAR Toolbox for Grouping Chemicals into Categories

March, 2018

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Report

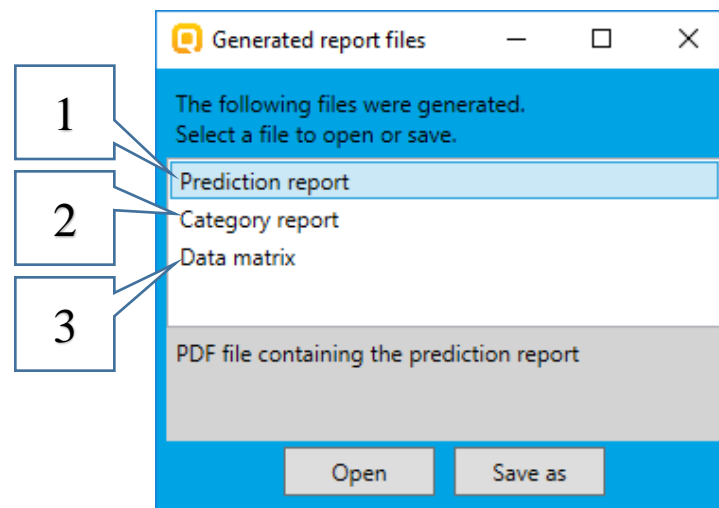
Generation of report

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 report

QSAR Toolbox prediction for single chemical

(in accordance with RAAF scenario 6)

The selected RAAF scenario is specified in the first page

(in accordance with RAAF scenario 6)

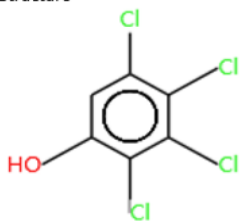
Date: 28 Mar 2018

Author(s):

Contact details:

Target information		
Structural information	Numerical identifiers	Chemical names
SMILES: Oc1cc(Cl)c(Cl)c(Cl)c1Cl	CAS#: 4901-51-3 Other: EC Number:3797243	2,3,4,5-Tetrachlorophenol henol Phenol, 2,3,4,5-tetrachloro- TETRACHLOROPHENOL, 2

Structure



Data matrix report

Structure	Neighbour #2	Neighbour #3	Neighbour #4	Neighbour #5
3 CAS number 4901-51-3	4901-51-3	87-86-5	58-06-2	88-06-2
4 Chemical name 2,3,4,5-Tetrachlorophenol	2,3,4,5-Tetrachlorophenol	Pentachlorophenol	CHLOROPHENOL, 2,3,4,6-	2,4,6-Trichlorophenol
5 Other identifier				
6 SMILES Oc1cc(Cl)c(Cl)c(Cl)c1Cl	Oc1cc(Cl)c(Cl)c(Cl)c1Cl	Oc1cc(Cl)c(Cl)c(Cl)c1Cl	Oc1cc(Cl)c(Cl)c(Cl)c1Cl	Oc1cc(Cl)c(Cl)c(Cl)c1Cl
7 Parameters unit				
8				
9				
10 Vapor Pressure (Antoine method) mm Hg	0.000136	0.0000757	0.000411	0.00573
11 Molecular Weight Da	231.87588	266.31794	231.87588	197.43382
12 log Kow	4.09	4.74	4.09	3.45
13 Boiling point °C	288.07	311.71	288.07	262.08
14 Water Solubility mg/L	28.89	9.59	17.9	121
15				
16 Profiles				
17 Profiles used for grouping/subcategorization				
Using of "Bat liver S9 metabolism simulator" compared parent and products requirements: No alert found<AND>Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes<AND>Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes<AND>AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes<AND>AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 4 metabolites; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 5 metabolites; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes	Parent and 2 metabolites; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes, Radical, Radical >> Radical mechanism via ROS formation (indirect), Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes

Predicted endpoint: Chromosome specified; No guideline specified
Predicted value: Positive
Unit/scale: Chromosome aberration
Data gap filling method: Read-across
Summary: manually editable field
 Not provided by the user

Category report

QSAR Toolbox report for category

1. Category definition

1.1. Category definition

Not provided by the user

manually editable field

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	unit (family)
	°C
	<no units>
	Da
	mm Hg
	mg/L

Properties#Water solubility; Physical Chemical
 #Vapour pressure; Physical Chemical

unit (family)
mg/L(Mass concentration)
mg/L(Mass concentration)
mg/L(Mass concentration)
°C(Temperature)
mm Hg(Pressure)
Pa(Pressure)

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 6.
- Note proficiency comes with practice.