

OECD QSAR Toolbox v.4.1

Tutorial illustrating new options for grouping
with metabolism

Outlook

- **Background**
- Objectives
- Specific Aims
- The exercise
- Workflow

Background

- Grouping with metabolism is a procedure for finding analogues accounting for metabolism activation of the chemicals;
- This is a step-by-step presentation designed to take the user through the new options for grouping with metabolism, implemented in QSAR Toolbox v.4.0.

Outlook

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Objectives

This presentation demonstrates a number of functionalities for searching of analogues accounting metabolism:

- Identify analogues based on the metabolites with:
 - common specific structure features;
 - common specific profiling results;
 - common specific parameter results.
- Identify analogues based on the parent and metabolites package.

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Specific Aims

- To familiarize the user with the map similarity options when define category with metabolism.

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The Exercise

- In this exercise we will search for suitable analogues of 1,2-Ethanediamine (CAS# 107-15-3) for predicting of skin sensitization potential.
- The target chemical have no a protein binding alert for skin sensitization.
- Skin metabolism of target chemical will be accounted for.
- Different map similarity options will be applied for defining a category.

Outlook

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Workflow

- As you know the Toolbox has 6 modules which are typically used in sequence:
 - Input
 - Profiling
 - Data
 - Category Definition
 - Data Gap Filling
 - Report
- In this example we will use only the first four modules, tailored to the aims of the example.

Outlook

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 - **Input**

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

Ways of Entering a Chemical

User Alternatives for Chemical ID:

A. Single target chemical

- Chemical Name
- Chemical Abstract Services (CAS) number (#)
- SMILES (simplified molecular information line entry system) notation
- Drawing chemical structure
- Select from User List/Inventory/Databases

B. Group of chemicals

- User List/Inventory
- Specialized Databases

Input Screen

Input target chemical by CAS#

The screenshot shows the QSAR Toolbox software interface. The main window has a menu bar with options like Document, Single Chemical, Chemical List, Search, and Target Endpoint. Below the menu bar is a toolbar with icons for New, Open, Close, Save, CAS#, Name, Structure Composition, Select, ChemIDs, Database Inventory, List, and Substructure. The main workspace is currently empty. A search dialog box is open, titled "Search by CAS #". The dialog box has a search field containing "107153" and a "Search" button. Below the search field are buttons for "Select All", "Unselect All", and "Invert Selection", and a status indicator "Selected 1 of 1". The search results are displayed in a table:

1	CAS	107-15-3
	SMILES	NCCN
	CS Relation	High
<input checked="" type="checkbox"/>	Substance	Mono constituent
	Composition	
	Name	1,2-diamino-ethane 1,2-DIAMINOETHANE 1,2-Ethanediamine

To the right of the table is a chemical structure diagram of 1,2-diaminoethane, showing a central carbon-carbon bond with two amino groups (H₂N and NH₂) attached to the carbons.

1. Click on **CAS#**; 2. Type **107153** in the blank field; 3. Press **Search**; 4. Confirm with “OK”

Outlook

- Background
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- **Workflow**
 - Chemical Input
 - **Profiling**

Profiling

Overview

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

Profiling

Profiling the target chemical

- The actual profiling will take up to several seconds depending on the number and type of profilers selected.
- Including of metabolic simulator is more time consuming.
- The results of profiling automatically appear under the target chemical
- This result will be used to search for suitable analogues in the next steps of the exercise.

Profiling

Profiling the target chemical

1. Click on Profiling; 2. Check the box in front of the *Protein binding alerts for skin sensitization by OASIS* profile; 3. Click on **Apply**; 4. No alert is found in the target structure.

Profiling

Profiling the target chemical

Profiling results for the target metabolites can be also retrieved.

1. Check the Skin metabolism simulator in addition to the selected profile. 2. Click on **Apply**; 3. Five metabolites are generated; 4. Structural alerts for SS are found in two of the metabolites.

Profiling

Explain of profiling results

The screenshot illustrates the workflow for explaining profiling results in the QSAR Toolbox. It shows the 'Profiling results' window with a tree view of alerts for 'Chemical 1 (NCCN)'. A right-click context menu is open over the results, with 'Explain' selected. A second right-click context menu is open over a specific alert, with 'Display chemicals' selected. The 'File' dialog box shows two chemical structures in separate windows, labeled '1' and '2'. The 'Save to smi' button is highlighted.

1. Right click over the found results and select **Explain** for more details. 2. Right click on the found alert and select **Display chemicals** to see for which structures alerts have been found; 3. The structures can be saved as *.smi* file. When you see them click on **OK**.

Outlook

- Background
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- **Workflow**
 - Input
 - Profiling
 - **Data**

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 Selecting databases

The screenshot displays the QSAR Toolbox interface. At the top, there are navigation icons for Input, Profiling, Data, Category definition, Data Gap Filling, and Report. Below this, there are buttons for Data, Import, and Export, with sub-options for Gather, Import, IUCLID6, and IUCLID6. The main workspace is divided into several panels:

- Documents:** Shows a document titled 'Document 1' with CAS number 107153.
- Databases:** A list of databases with checkboxes. 'Skin sensitization' and 'Skin sensitization ECETOC' are checked and highlighted with a red box.
- Inventories:** A list of inventories with checkboxes, including Canada DSL, COSING, DSSTOX, ECHA PR, and FINECS.
- Filter endpoint tree...:** A tree view of endpoints. 'Human Health Hazards' is expanded, showing sub-categories like Acute Toxicity, Bioaccumulation, Carcinogenicity, etc. 'Sensitisation' is highlighted in blue.
- Structure:** Shows the chemical structure of ethylamine (CCN).
- 1 [target]:** A table with one row containing the chemical structure.

A blue callout box at the bottom of the screenshot contains the text: "Select Skin sensitization and Skin sensitization ECETOC databases".

Outlook

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- **Workflow**
 - Input
 - Profiling
 - Data
 - **Category definition**

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.
- A category can be defined with and without metabolism.
- Grouping with accounting for metabolic transformation is a procedure for finding analogues accounting metabolism activation of the chemicals.

Category definition

Define with metabolism

1

2

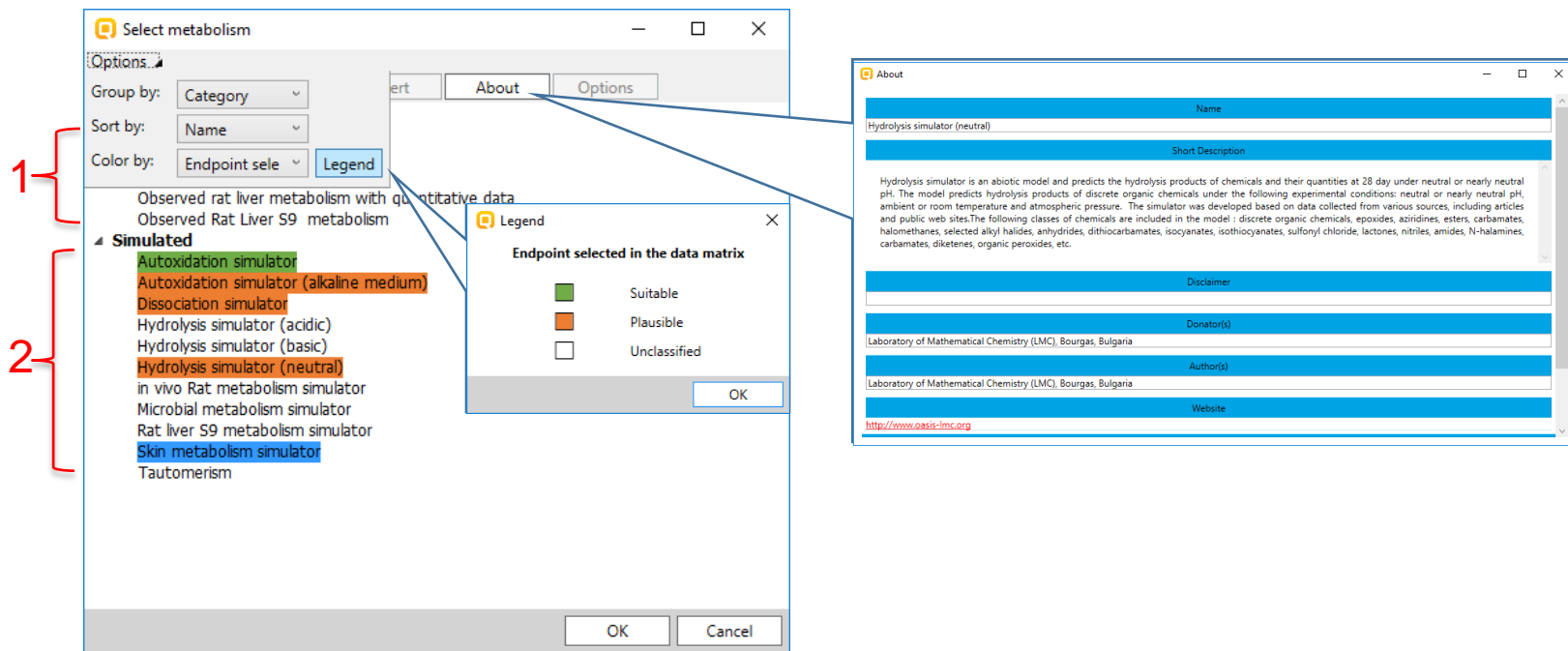
3

4

1. Go to *Category definition*; 2. Click on **Sensitization** endpoint; 3. **Define with metabolism**; 4. Select **Skin metabolism simulator**

Category definition

Sidebar on defining with metabolism



All available transformation maps – documented (1) and simulated (2) in Toolbox can be used in the primary data grouping. The maps are colored if a target endpoint is selected in the data matrix. Short description for each of the metabolic transformations can be seen by click on About.

Category definition

Define with metabolism

When the transformation map is selected, the “Map similarity options” dialogue appears. It shows all the generated metabolites of the target chemical by the simulator that was preliminary selected. The dialogue has two subsections:

- First subsection (1) shows parent and each of the generated metabolites (by the preliminary selected metabolism simulator) in separate rows. This allows defining of different criteria for each of structures for finding analogues.
- Second subsection (2) is working with whole package “parent + metabolites”, i.e. the criteria is provided for the whole package but not for separate metabolite.

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

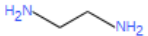
See on the next slide.

Category definition

Define with metabolism

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent 	none	No criteria.
Metabolite 1 NH ₃	none none exact parametric profile structural	All chemicals
Parent & Metabolites	none	No criteria.

OK Cancel

1

2

3

Category definition

Define with metabolism

Explanation of different options from the drop down menu:

- **None** – default options; no criteria is set;
- **Exact** – provides opportunity to search for metabolites in the analogues having exact to the specified metabolite structure; only available for the metabolites and the package “parent + metabolites” but not for the parent chemical;
- **Parametric** – to have specific value or range of variation of defined parameter (a list with all parameters currently available in the Toolbox is provided);
- **Profile** – to have specific category by selected profiler (a list with all profilers is provided);
- **Structural** – to have specific similarity based on the atom centered fragments.

Category definition

Define with metabolism – Case 1

Different map similarity options will be examined.

Case 1: Searching of analogues based on a metabolite with defined profile

As you remember, structural alerts have been found for only two of the generated metabolites (*slide 21*).

The alerts are identical and therefore we can choose only one of the structures.

Category definition

Define with metabolism – Case 1

In order to find analogues based on metabolites with common profiling result, you have to follow the described steps below:

1. On the row with the target metabolite select a query which you will use for searching. Select “**profile**” as a criteria for the third metabolite. New drop-down menu with all available profiles appears;
2. Select *Protein binding alerts for skin sensitization by OASIS* from the drop-down menu;
3. You can see the found alerts in the metabolite by click on the **Edit** button. If more than one alert is available, the user can select whether they will search analogues with all or only one of the alerts.
4. In this case there is only one structural alert and we click on **OK**.
5. When you are ready click on the **OK** button

See the illustrated steps on the next slide.

Category definition

Define with metabolism – Case 1

The image shows the 'Map similarity options' dialog in the QSAR Toolbox. It contains a table with columns for 'Chemical', 'Query', and 'Criteria'. The table lists 'Parent' and three 'Metabolite' entries. Metabolite 3 is highlighted with a red box. A secondary dialog, 'Schiiff base formation', is open over Metabolite 3, showing target categories and profile options. Five numbered callouts (1-5) point to specific UI elements: 1 points to the 'profile' dropdown menu; 2 points to the 'Options: Edit' button; 3 points to the 'Criteria' column for the Parent row; 4 points to the 'OK' button in the secondary dialog; 5 points to the 'OK' button in the main dialog.

Chemical	Query	Criteria
Parent <chem>NCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NC=O</chem>	profile	Profiler: Protein binding alerts for skin sensitization by OASIS v... Options: Edit
All chemicals		
	none	No criteria.

Secondary Dialog: Schiiff base formation

Target: Schiiff base formation
 Schiiff base formation >> Schiiff base formation with carbonyl compounds
 Schiiff base formation >> Schiiff base formation with carbonyl compounds >> Aldehydes

Profiles (N/A):
 Acylation
 Acylation >> (Thio)carbamylation of protein nucleophiles
 Acylation >> (Thio)carbamylation of protein nucleophiles >> Isocyanates, Isothiocyanates
 Acylation >> Acyl transfer via nucleophilic addition reaction

Combine profiles:
 AND OR
 Invert result
 Strict

Category definition

Define with metabolism – Case 1

235 analogues are found. You can return to the profiling section and to check whether the found structures correspond to the defined query.

1

2

3

2

1. Go to *Profiling* section; 2. Check the used profile and metabolism (*Protein binding alerts for SS by OASIS plus Skin metabolism simulator*); 3. Click on **Apply**. You can see that all of the found analogues produce one or more metabolites with the searched alert.

Structure	1 [target]	2	3	4	5	6	7
Structure	<chem>NCCCN</chem>	<chem>C1CCNCC1</chem>	<chem>C1CCNCC1</chem>	<chem>C1CCNCC1</chem>	<chem>C1CCNCC1</chem>	<chem>C1CCNCC1</chem>	<chem>C1CCNCC1</chem>
Profile							
Endpoint Specific							
Metabolism/Transformations							
Endpoint Specific							
5 metabolites	3 metabolites	6 metabolites	7 metabolites	4 metabolites	4 metabolites	4 metab	
1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff
1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff
2 x Schiff base formatio	1 x Schiff base formatio	2 x Schiff base formatio	2 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff base formatio	1 x Schiff
2 x Schiff base formatio	2 x No alert found	2 x Schiff base formatio	2 x Schiff base formatio	6 x No alert found	3 x No alert found	3 x No alert found	1 x Schiff
3 x No alert found		4 x No alert found					3 x No a

Tutorial_24_New options for grouping with metabolismTB4.0 [Compatibility Mode] - Microsoft PowerPoint

Category definition

Define with metabolism – Case 2

Case 2: Searching of analogues with a common metabolite

With the “**Exact**” option the user can search analogues, which have a metabolite exactly the same as the selected.

Category definition

Define with metabolism – Case 2

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NCC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NCC=O</chem>	exact none exact parametric profile structural	Matches exact structure.
Parent & Metabolites	none	No criteria.

OK Cancel

Go to the metabolite of interest;
Select the **exact** option from the drop-down menu (1) and click on OK (2).

Category definition

Define with metabolism – Case 2

One analogue is found in the selected databases.
 To check whether the found structures correspond to the defined criteria, i.e. to produce the exact metabolite, you have to follow the steps:

1. Right click over the found structure and select **“Set as new target”**;

The screenshot displays the QSAR Toolbox interface. The top navigation bar includes 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Report'. Below this, the 'Categorize' section has options for 'Define', 'Define with metabolism', 'Subcategorize', and 'Combine'. The 'Documents' panel on the left shows a tree structure for 'Document 1' containing 'CAS: 107153' and two sub-items: 'Grouping with metabolism: Skin metabolism simulator'. The main workspace features a 'Filter endpoint tree...' on the left, a 'Structure' input field, and two columns for target structures. The first column shows the chemical structure of ethylenediamine (NCCN). The second column shows the chemical structure of piperazine (C1CCNCC1). A context menu is open over the piperazine structure, with the 'Set as new target' option highlighted. A callout box with the number '1' points to this option.

Category definition

Define with metabolism – Case 2

2. Right click over the new target and select:
Multiplication >> Metabolism/Transformations >> Skin metabolism simulator

The screenshot displays the QSAR Toolbox interface during the 'Category definition' step. The top navigation bar includes 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Report'. The 'Categorize' sub-menu is active, showing 'Define', 'Define with metabolism', 'Subcategorize', and 'Combine'. In the 'Documents' panel, a chemical structure is selected, and a context menu is open. A callout box with the number '2' indicates the right-click action. The menu path 'Multiplication > Metabolism/Transformations > Skin metabolism simulator' is highlighted. The 'Filter endpoint tree...' panel on the right shows a list of simulation endpoints, with 'Skin metabolism simulator' highlighted at the bottom.

Category definition

Define with metabolism – Case 2

A parent list (1) (consists of the target structure and all generated metabolites) with six child lists (2) (for each of the metabolites) are created. You can see that the searched metabolite is there.

The screenshot shows the QSAR Toolbox interface with the 'Category definition' workflow active. The 'Documents' panel on the left shows a parent list (1) and six child lists (2). The main workspace displays a table of metabolites, with 'metabolite #3' highlighted in a red box. The chemical structure of metabolite #3 is shown as H₂N-CH₂-CHO.

Parent structure	metabolite #1	metabolite #2	metabolite #3	metabolite #4	metabolite #5	metabolite #6
<chem>C1CCNCC1</chem>	<chem>N</chem>	<chem>NC(=O)O</chem>	<chem>NC=O</chem>	<chem>NCN</chem>	<chem>O=CC=O</chem>	<chem>OC(=O)C=O</chem>
Structure info						
Parameters						
Physical Chemical Properties						
Environmental Fate and Transport						
Ecotoxicological Information						
Human Health Hazards						

Category definition

Define with metabolism – Case 3

Case 3: Searching of analogues based on a metabolite with defined parameter value

With this option you can search analogues of the target chemical, which have metabolite(s) with defined parameter value.

When the parameter of interest is selected, it is automatically calculated for the current metabolite.

Category definition

Define with metabolism – Case 3

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NCC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NCC=O</chem>	parametric	Calculator: [dropdown] [operator] [value]
Metabolite 4		
Parent & Metabolites	none	

Go to the metabolite of interest; Select the **parametric** option from the drop-down menu (1). New calculator drop-down menu appears. Select **log Kow** (2). You can use and the filter option to find your parameter more quickly.

Category definition

Define with metabolism – Case 3

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NCC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NCC=O</chem>	parametric	Calculator: log Kow = -1.64
Metabolite 4		
Parent & Metabolites	none	No criteria.

OK Cancel

The parameter value is calculated automatically for the target metabolite (1). Then the user can decide to search with the exact value, to use any of the mathematical symbols or to search parameter values in a range (2).

Category definition

Define with metabolism – Case 3

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NC=O</chem>	parametric	Calculator: log Kow range From: -1.6 To: -1.68
Metabolite 4		
All chemicals		
Parent & Metabolites	none	No criteria.

OK Cancel

We will select to search in a range (1). As you remember the calculated *logKow* value for the target metabolite is **-1.64**. Therefore, we will search analogues, which have metabolite(s) with similar *logKow* values. In this example we define a range from **-1.6** to **-1.68** (2). Click on **OK** to execute the search.

Note: It will take up to several minutes if you make this example for first time.

Category definition

Define with metabolism – Case 3

27 analogues are found in the selected databases. Each of these structures posses metabolite(s) with logKow value in the previously defined range.

The screenshot displays the QSAR Toolbox software interface during the 'Category definition' process. The top navigation bar includes options for Input, Profiling, Data, Category definition (selected), Data Gap Filling, and Report. The left sidebar shows 'Documents' with 'Case 3' and 'CAS: 107153' selected, and 'Grouping methods' with 'Predefined' and 'General Mechanistic' categories. The central panel shows the 'Filter endpoint tree...' with various endpoints like 'Acute Toxicity', 'Bioaccumulation', and 'Toxicity to Reproduction'. The main data table displays chemical structures and their classification results across 9 columns.

1 [target]	2	3	4	5	6	7	8	9
M: Ambiguous	M: Positive	M: Positive	M: Negative	M: Positive	M: Positive	M: Negative	M: Positive	M: Positi

Category definition

Define with metabolism – Case 4

Case 4: Searching of analogues based on similar metabolites

We can search for analogues of our target chemical, which have metabolites structurally similar to the defined one.

1. Select **structural** option from the drop-down menu for the target metabolite;
2. The default settings could be seen by click on the **Options** button.
3. Close the window by **X** button;
4. Define the similarity threshold.

See the illustrated steps on the next slide.

Category definition

Define with metabolism – Case 4

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NC=O</chem>	structural	Similarity ≥ 0 %
Metabolite 4		
Parent & Metabolites	none	No criteria.

Similarity options

Measure

- Tanimoto (Jaccard)
- Dice
- Kulczynski-2
- Ochiai(Cosine)
- Yule

Molecular features

- Atom pairs
- Topologic torsions
- Atom centered fragments
- Path
- Cycles
- PubChem features

Options

Formula

$$\frac{c}{0.5 [(a + b) + (b + c)]}$$

Description

Example

A	B	C
2	2	10

Similarity = 83.333% [Details](#)

Calculation

- Fingerprint
- Hologram

Average by features

- Average by features
- Combine all features

Atom characteristics

- Atom type
- Count H attached
- Count heavy atoms attached
- Hybridization
- Incident pi-bonds
- Valency
- Charge
- Cyclic

Annotations: 1 points to the 'structural' dropdown; 2 points to the 'Options' button; 3 points to the 'Hologram' radio button; 4 points to the 'Similarity ≥ 0 %' field.

Category definition

Define with metabolism – Case 4

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NCC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NCC=O</chem>	structural	Similarity >= 50 % Options
Metabolite 4		
Parent & Metabolites	none	No criteria.

All chemicals

OK Cancel

1. Select **structural** option from the drop-down menu;
2. Define similarity threshold of $\geq 50\%$ according to the default options;
3. Click on **OK** to execute the query.

Category definition

Define with metabolism – Case 4

15 analogues are found in the selected databases. Each of them possesses metabolite(s) similar 50% or more to the structure of the previously selected metabolite.

The screenshot displays the QSAR Toolbox software interface during the 'Category definition' process. The 'Documents' panel on the left shows 'Case 4' with CAS: 107153 and a selected grouping method 'Grouping with metabolism: Skin metabolism simulator'. The 'Filter endpoint tree...' panel on the right lists various toxicological endpoints, with 'Sensitisation' selected. The main workspace displays a table with 7 columns representing different chemical structures and rows for various endpoints. The 'Sensitisation' row shows 'M: Ambiguous' for the first structure and 'M: Positive' for the others. A red box highlights the number '15' in the bottom left corner of the interface.

Category definition

Define with metabolism – Case 5

Case 5: Searching of analogues based on defined criteria for the package “target and metabolites”

The user can select a profiling, parametric or structural query for both – target and its metabolites.

In this example we will search only for analogues with defined profile.

Category definition

Define with metabolism – Case 5

1. Select a profile option for the package “parent & metabolites”;
2. Select *Protein binding alerts for SS by OASIS* profile;
3. Click on the **Edit** button. All found alerts in the parent structure and its metabolites are shown.
4. Check “**strict**” option to search only analogues with exact match these alerts.
5. Click on “**OK**” button to confirm the defined searching criteria.
6. Click on “**OK**” button in the general Map similarity options window to execute the search.

See the illustrated steps on the next slide.

Category definition

Define with metabolism – Case 5

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1 <chem>N</chem>	none	No criteria.
Metabolite 2 <chem>NCC(=O)O</chem>	none	No criteria.

Parent & Metabolites: profile

Profiler: Protein binding alerts for skin sensitization by OASIS

Options: **Edit**

Combine

AND OR Invert result Strict

Target

No alert found

Schiff base formation

Schiff base formation >> Schiff base formation with carbonyl compounds

Schiff base formation >> Schiff base formation with carbonyl compounds >> Alde...

Down Up Reset Options

Profiles

(N/A)

Acylation

Acylation >> (Thio)carbamoylation of protein nucleophiles

Acylation >> (Thio)carbamoylation of protein nucleophiles >> Isocyanates, Isothio...

Acylation >> Acyl transfer via nucleophilic addition reaction

Acylation >> Acyl transfer via nucleophilic addition reaction >> Carbodiimide...

OK Cancel

OK Cancel

Category definition

Define with metabolism – Case 5

10 structures are retrieved. Only the searched structural alerts are found either in the parent structure or in the structures of its metabolites.

The screenshot shows the QSAR Toolbox interface with the 'Category definition' workflow selected. The 'Filter endpoint tree' is expanded to 'Skin metabolism simulator'. A table displays results for five target structures (1-5). The table includes columns for target structures, metabolite counts, and detected alerts.

Target	1 [target]	2	3	4	5
Structure	<chem>NCCCN</chem>	<chem>C1CCNCC1</chem>	<chem>CCN(C)CCN</chem>	<chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem>	<chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem>
Human Health Hazards					
Sensitisation	M: Ambiguous	M: Positive	M: Positive	M: Positive	M: Negative
Metabolism/Transformations	No alert found	No alert found	No alert found	Schiiff base formatio	No alert found
Metabolites	5 metabolites	6 metabolites	12 metabolites	23 metabolites	19 metabolites
Alerts	1 x Schiiff base formz 1 x Schiiff base formz 2 x Schiiff base formz	1 x Schiiff base formz 1 x Schiiff base formz 2 x Schiiff base formz	1 x Schiiff base formz 4 x Schiiff base formz 5 x Schiiff base formz	10 x Schiiff base formz 14 x Schiiff base formz 14 x Schiiff base formz	1 x Schiiff base formz 11 x No alert found 7 x Schiiff base formz

Category definition

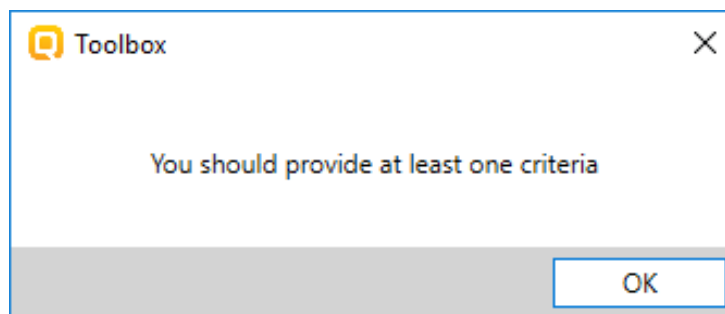
Define with metabolism – Case 6

Case 6: Searching of analogues based on combination of queries

The user can search for analogues with combination of different criteria for each of the metabolites as well as the parent structure.

Note: The user can search for analogues based on any of the target characteristics (profiling result, parameter value or structural similarity) and at least one other criteria for a metabolite.

If a criteria is set for the parent structure only, informing message will appear:



Category definition

Define with metabolism – Case 6

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In addition the Toolbox user can select whether all defined queries to be searched together (1) or at least one of them (2).

Map similarity options

All queries At least one

Chemical	Query	Criteria
Parent <chem>NCCN</chem>	none	No criteria.
Metabolite 1		

Category definition

Define with metabolism – Case 6

Now we will search for structures which have simultaneously:

- Parent structure similar to the target structure;
- Exact metabolite structure;
- Metabolite with defined profile.

Category definition

Define with metabolism – Case 6

Chemical	Query	Criteria
Parent <chem>CCN</chem>	structural	Similarity 2 50% Options
Metabolite 1 <chem>N</chem>	exact	Matches exact structure.
Metabolite 2 <chem>NC(=O)O</chem>	none	No criteria.
Metabolite 3 <chem>NC=O</chem>	profile	Protein binding alerts for skin sensitization by OASIS v... Options: Edit
Metabolite 4		
All chemicals		
Parent & Metabolites	none	No criteria.

1. Select **structural** option from the drop-down menu for the parent; Set **50%** threshold with default options;
2. Select **exact** option from the drop-down menu for the first metabolite;
3. Select **profile** option and *Protein binding alerts for skin sensitization by OASIS profile* from the drop-down menus for the third metabolite.
4. Click on **OK** to execute the search.

Recap

In short, grouping with metabolism in Toolbox 4.0 allows finding analogues that have:

- metabolite with defined profile
- exact metabolite
- metabolite with defined parameter value
- metabolite similar to defined one
- parent and its metabolites with defined profile, parameter value or structural similar
- combination of above

Congratulation

- You have now been familiarized with different map similarity options for grouping with metabolism.
- Note proficiency comes with practice.