QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

OECD QSAR Toolbox v.4.1

Tutorial illustrating quantitative metabolic information and related functionalities

Outlook

- **Aim**
- Background
- Example for:
  - Visualizing quantitative data within Toolbox user interface
  - Application of quantitative metabolic data in data gap filling

Aim

The implementation of quantitative metabolic information and related functionalities in Toolbox aim to expand and facilitate the usage of metabolic information.

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- **Background**
- Examples for:
  - Visualizing quantitative data within Toolbox user interface
  - Application of quantitative metabolic data in data gap filling

Background

The documented/simulated metabolic information available in Toolbox is expanded by adding quantitative data and developing tools for using this type of information for grouping or pruning existing categories.

Outlook

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- **Examples for:**
  - **Visualizing quantitative data within Toolbox user interface**
  - Application of quantitative metabolic data in data gap filling

Visualizing quantitative data within Toolbox user interface:

Steps

- Chemical input
- Profiling

Chemical Input

- 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.

Chemical Input
Ways of Entering a Chemical

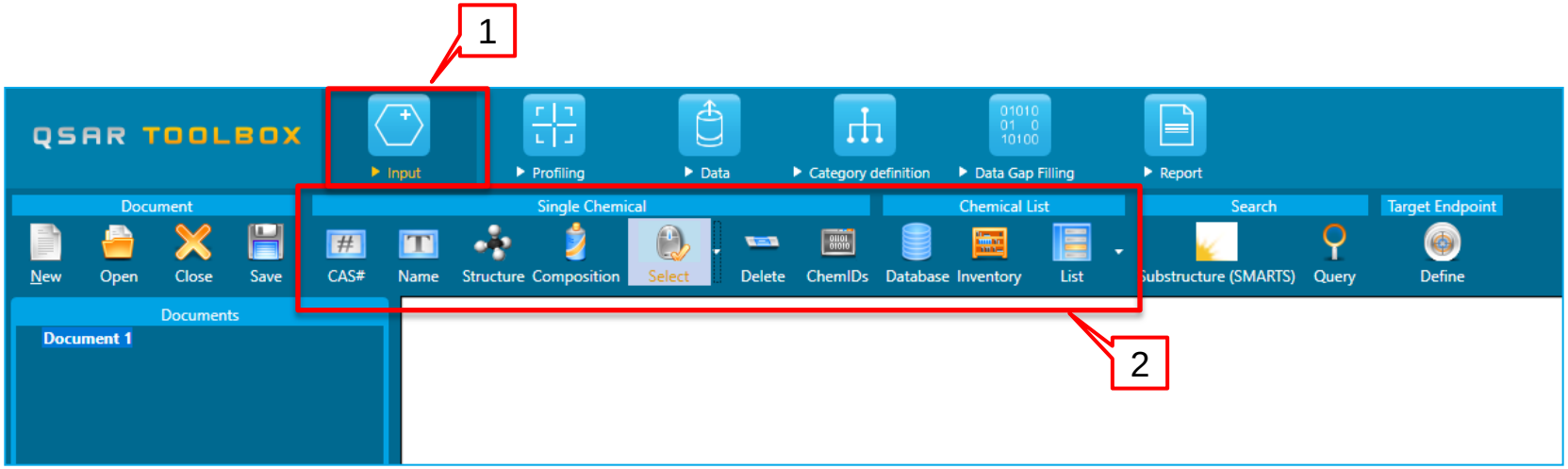
Single target chemical

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

Chemical Input:
Single target chemical

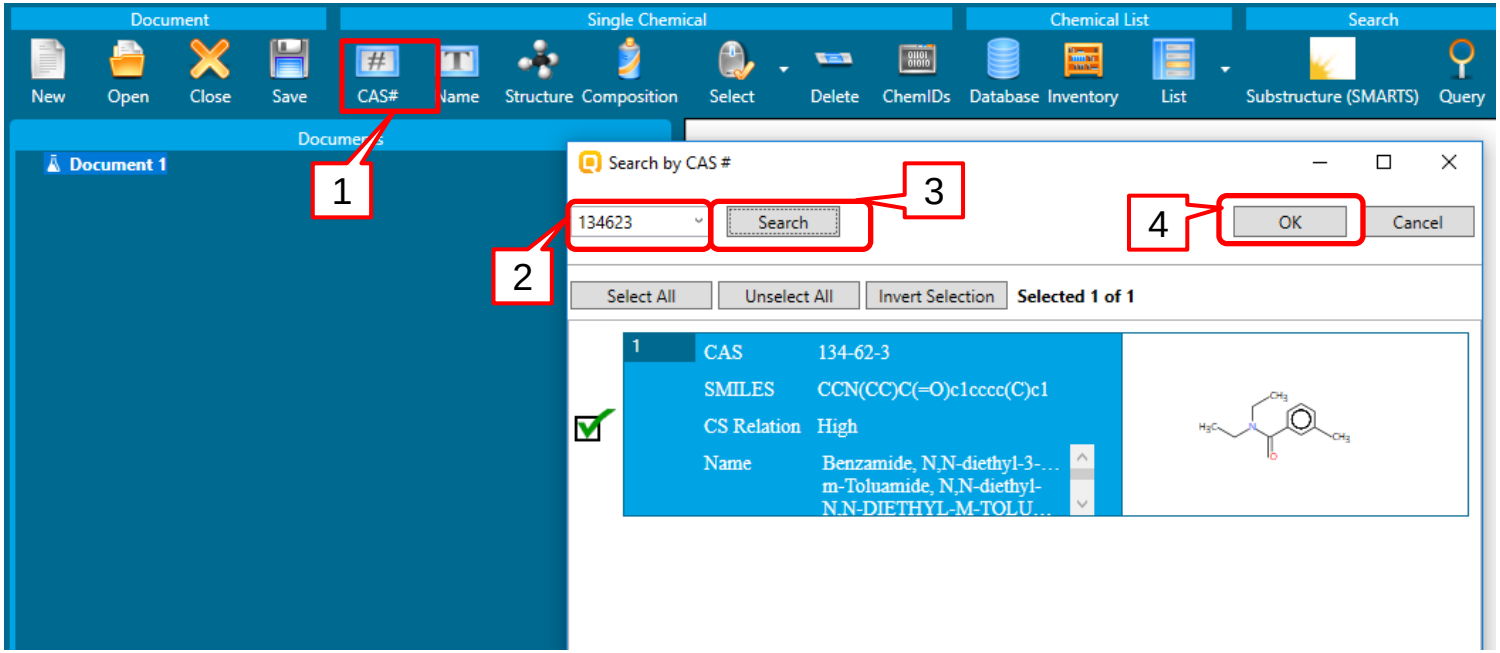
- Open the Toolbox.
- Click on “Input” (see next screen shot).

Chemical Input
Single target chemical



1. Click on *Input (1)* to display the main Input section (2).

Single target chemical
by CAS RN 134-62-3



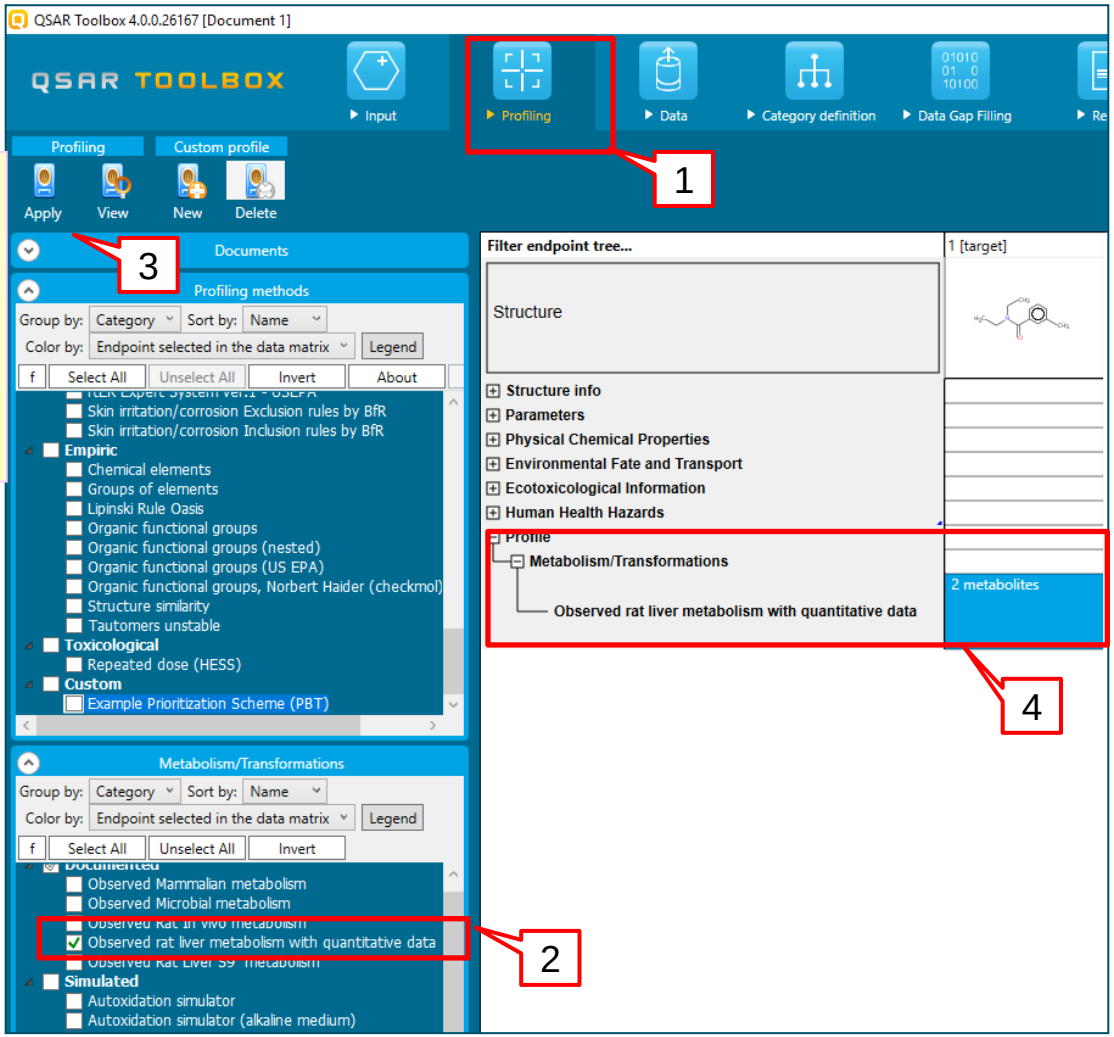
1. Press CAS# (1); 2. Type in the CAS # (2) ; 3. Click on *Search* (3);
4. Press *OK* (4).

Profiling
Overview

- "Profiling" refers to the electronic process of retrieving relevant information on a compound which is stored in the Toolbox, other than its fate and (eco)toxicity data.
- Toolbox has many predefined profilers but it also allows the user to develop new profilers.

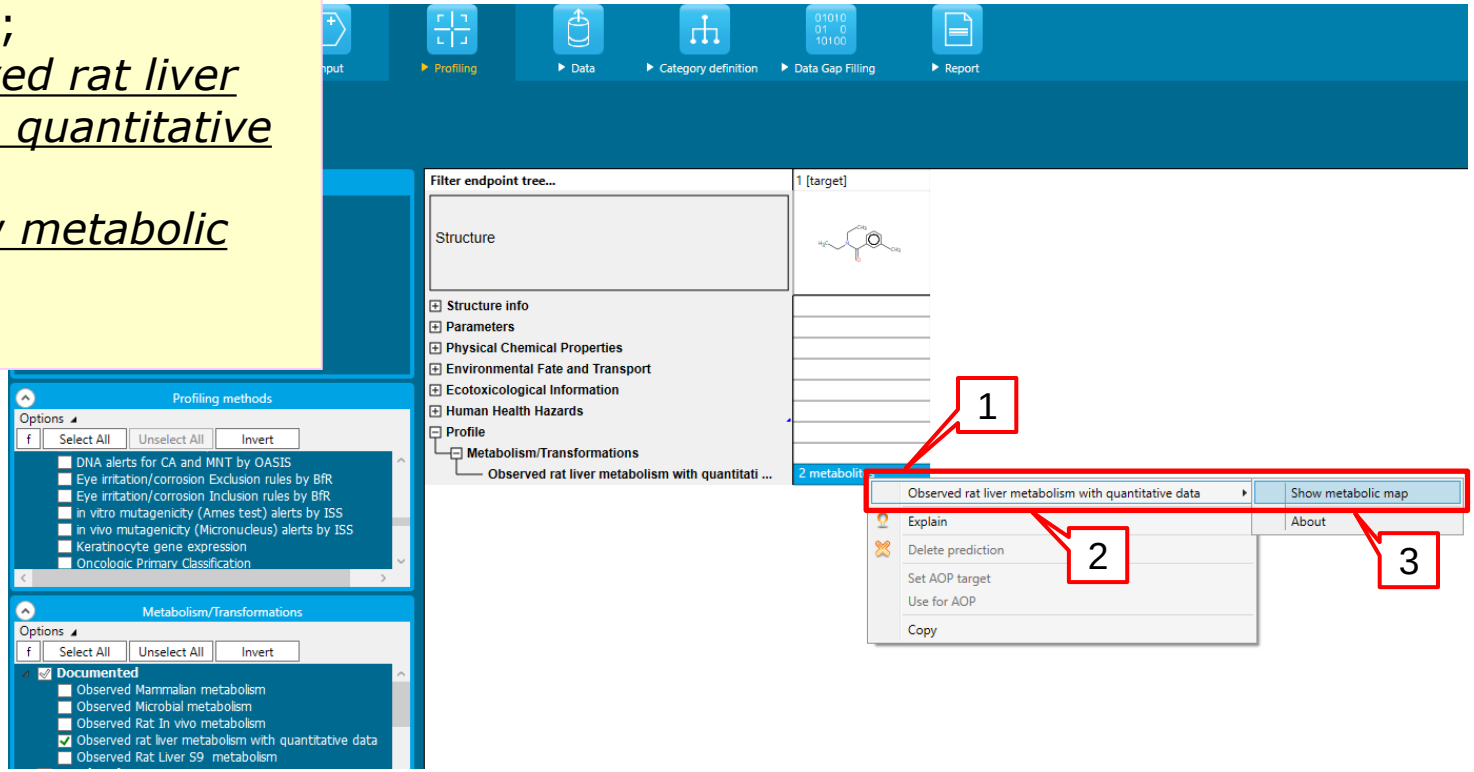
Profiling

1.Select Profiling(1);
2. Tick *Rat liver metabolism with quantitative data* (2);
3. Click on *Apply* (3);
4. Two metabolites are generated (4).

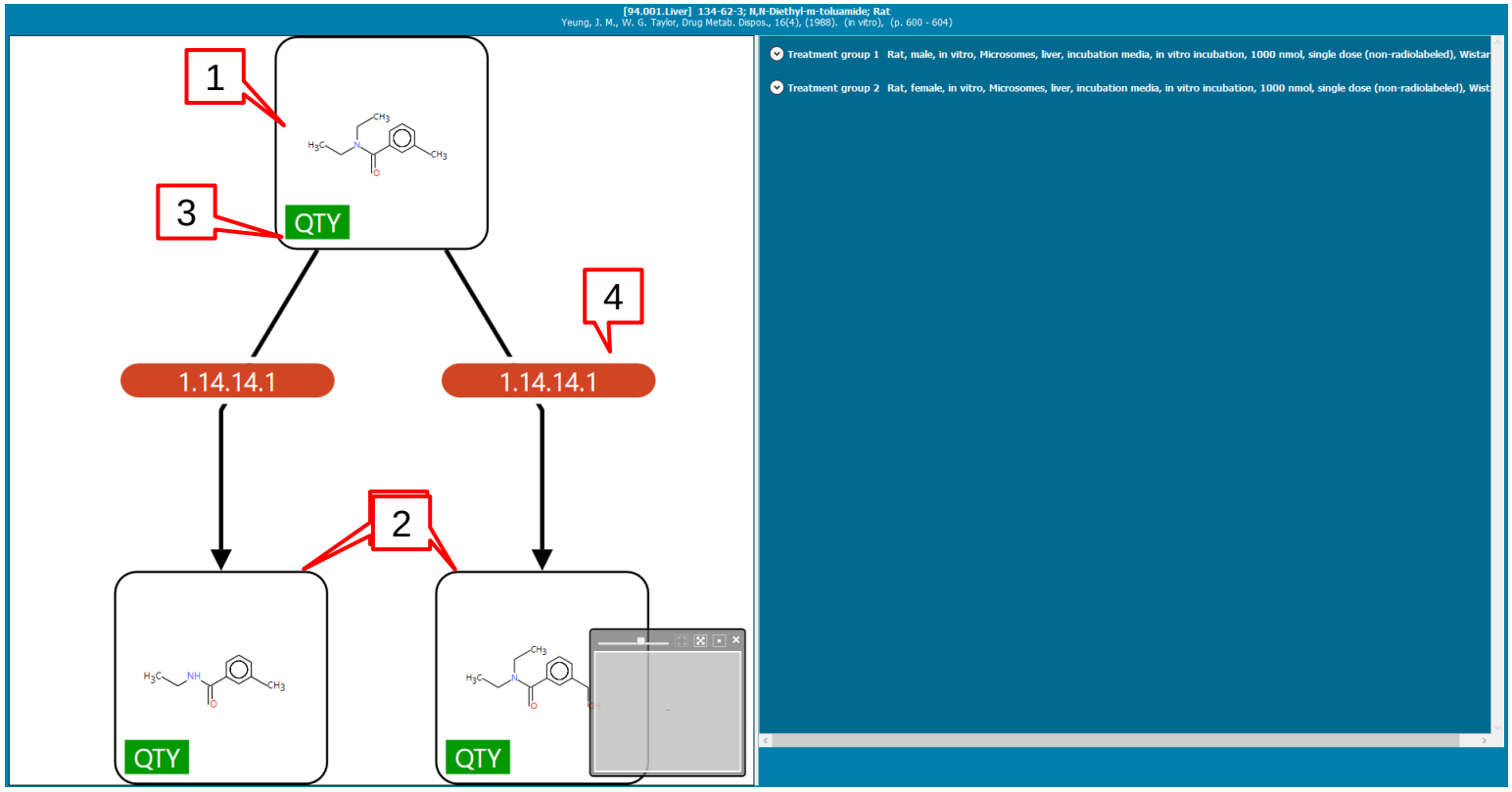


Profiling

1. Right click on the Profiler outcome cell (1);
2. Select *Observed rat liver metabolism with quantitative data* (2);
3. Click on *Show metabolic map* (3).

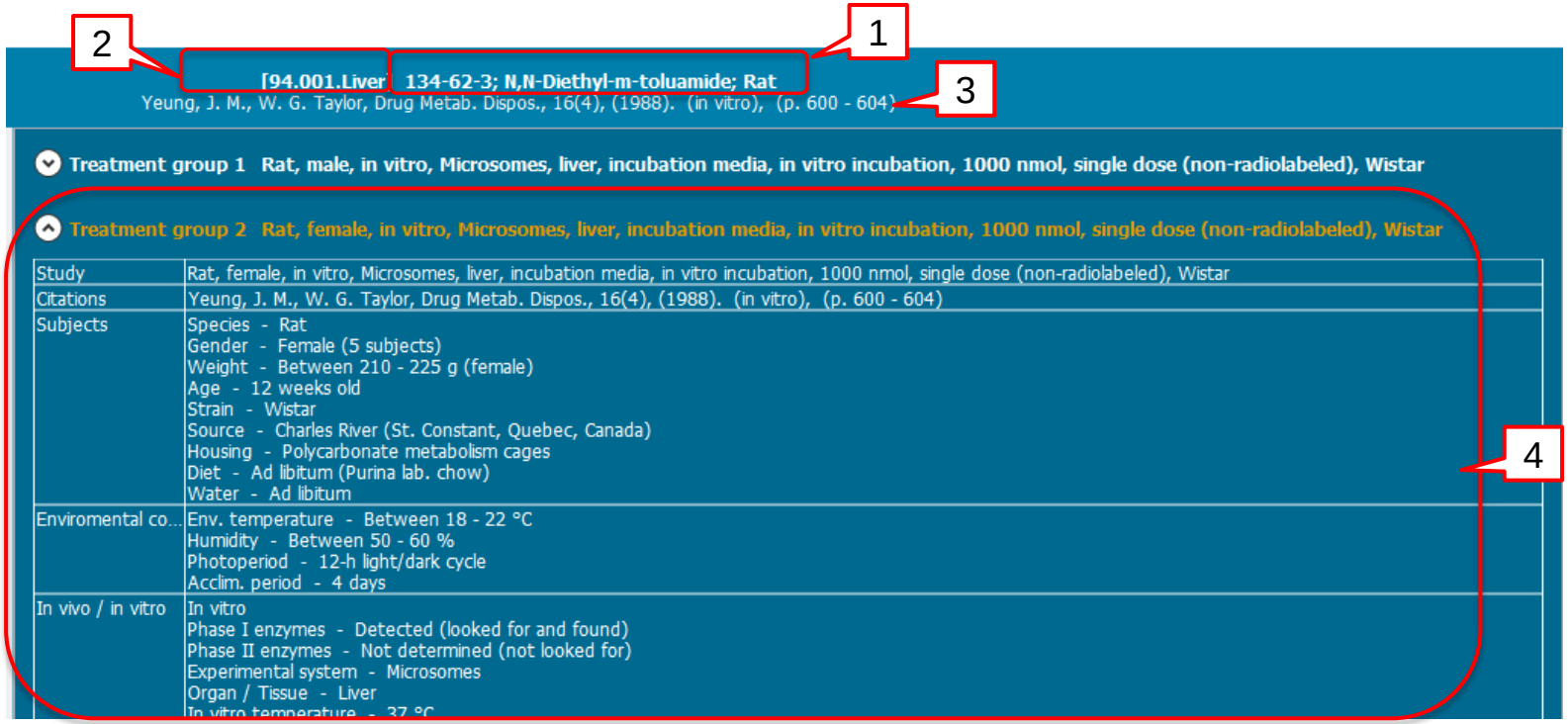


Profiling



- The target (1) and the generated metabolites(2) are shown.
- Quantity label "**QTY"** indicates that there are some quantitative data for the target/metabolite (3)
- Label "1.14.14.1" indicated enzymatic information, which could be seen in METAPATH software(4)

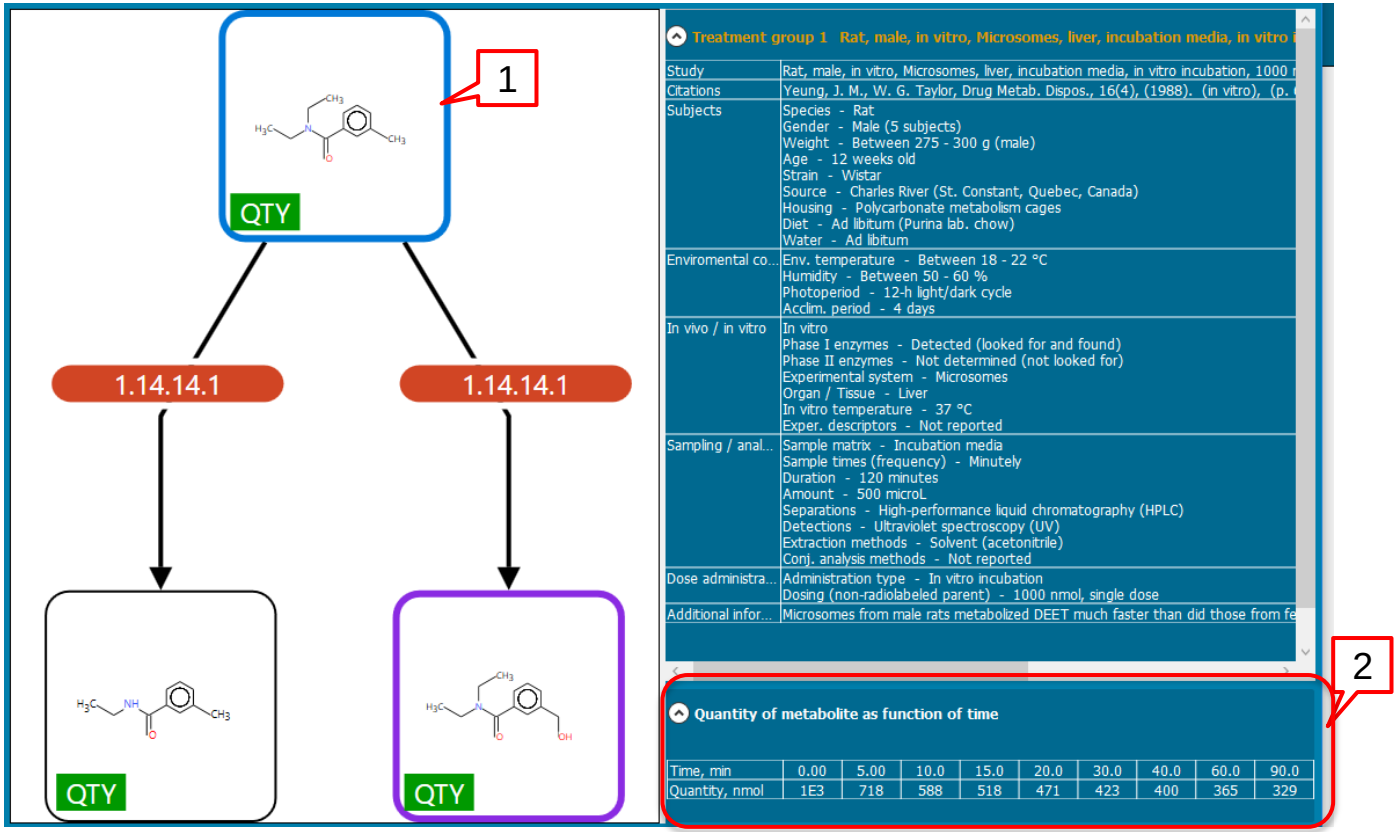
Profiling



The feature of top and right panel are:

- Information about the target chemical (1);
- Map number generated in the METAPATH software(2);
- The reference from which the data is taken is also included (3);
- Detailed information about the treatment groups is displayed upon expansion (4).

Profiling



- Once the treatment group is expanded, make left mouse click on a target/metabolite (1) to see its quantity as a function of time (2).

Outlook

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  - **Application of quantitative metabolic data in data gap filling**

Application of quantitative metabolic data in data gap filling:

Steps:

- Input list of chemicals
- Gathering of experimental data for skin sensitization
- Data gap filling

Application of quantitative metabolic data in data gap filling

- In this tutorial only a working example illustrating this functionality is shown.
- 13 chemicals with quantitative data are used.
- We are fully aware that this example is not well defined , however its aim is to only introduce you to this functionality.

Data gap filling
An overview

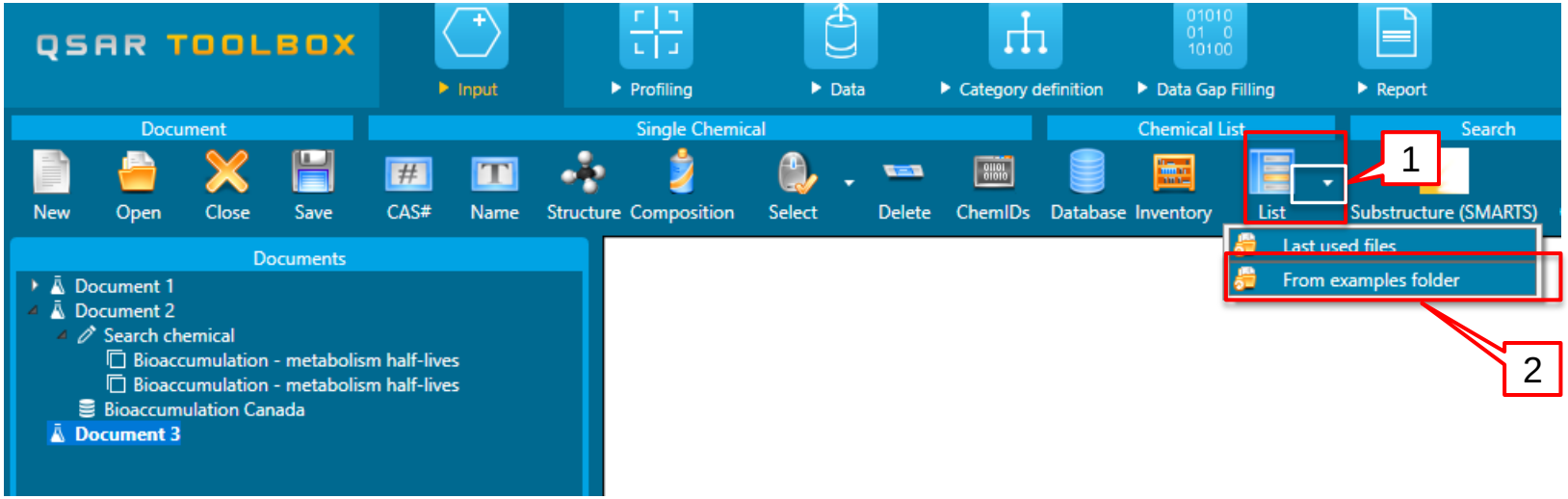
- Data Gap Filling (DGF) module gives access to three different data gap filling tools:
  - Read-across
  - Trend analysis
  - (Q)SAR models

- 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.

Application of quantative metabolic data in data gap filling

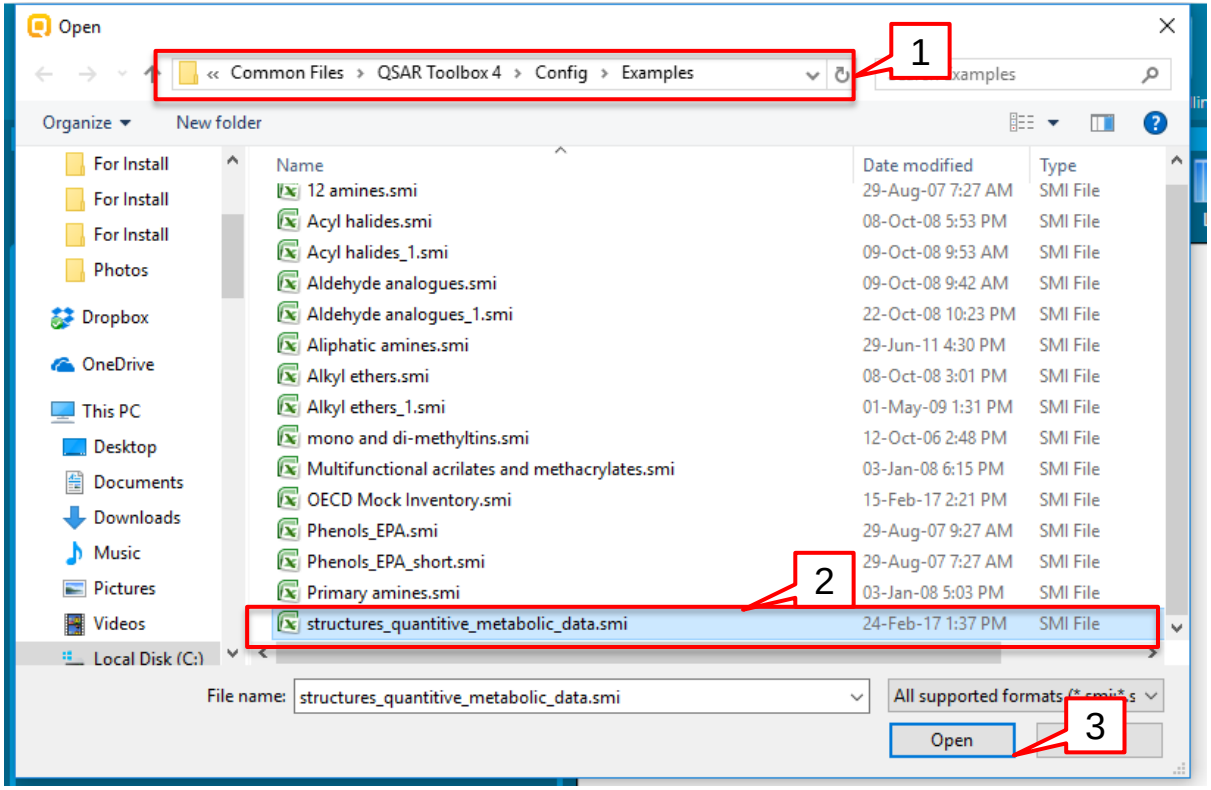
- Quantitative metabolic data could be used to filter analogues in data gap filling.
- Quantities cannot be used directly to filter out chemicals (quantities are not single values, but time series; often data comes in units, which are not convertible - i.e. mol/L vs mol/g protein).
- In this respect a reliable measure that can be used for filtering is the half-life of parent chemicals calculated from quantitative data.
- As a result a new calculator "Half-Life (observed metabolism)" was implemented.

Input list of chemicals



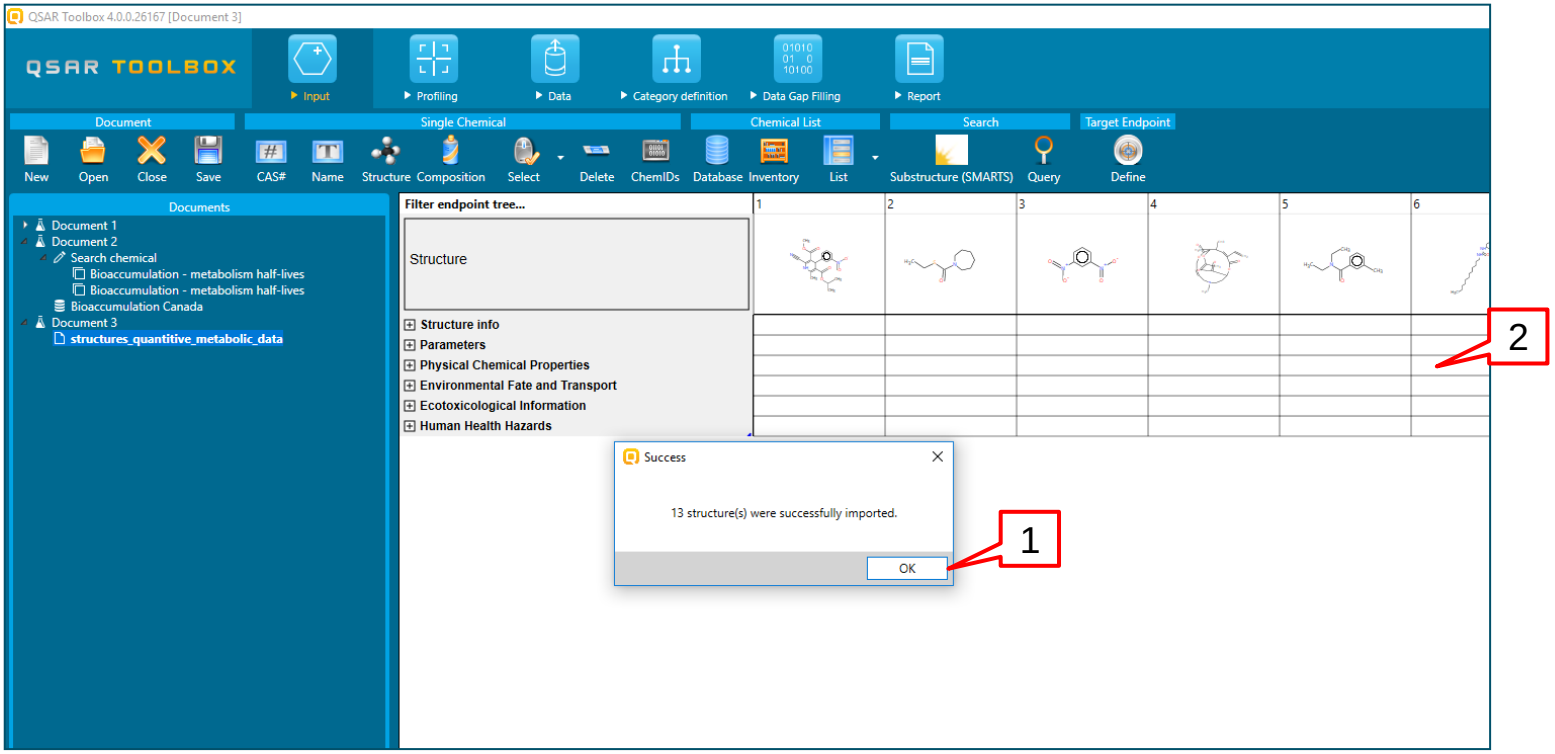
1. Open the drop-down menu of List button (1)
2. Select *From Example folder* (2)

Input list of chemicals



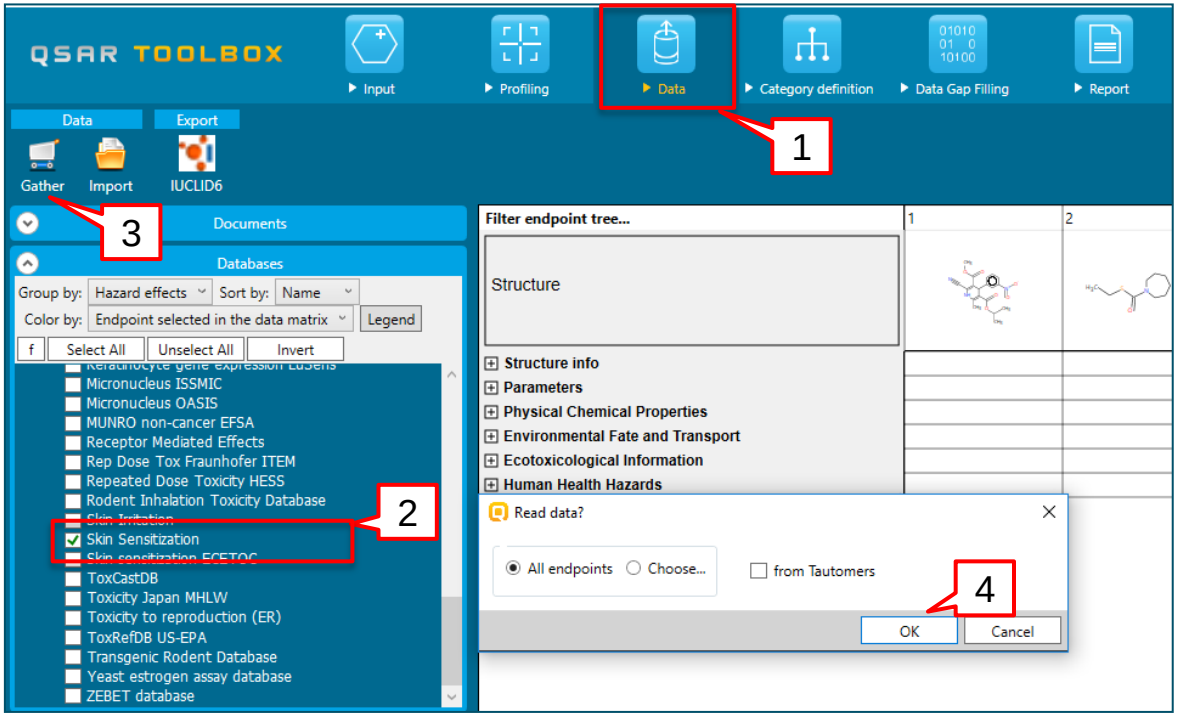
1. Examples folder directory in Toolbox is open (1);
2. Select *structure_quantative_metabolic_data.smi*(2);
3. Click on *Open* (3)

Input list of chemicals



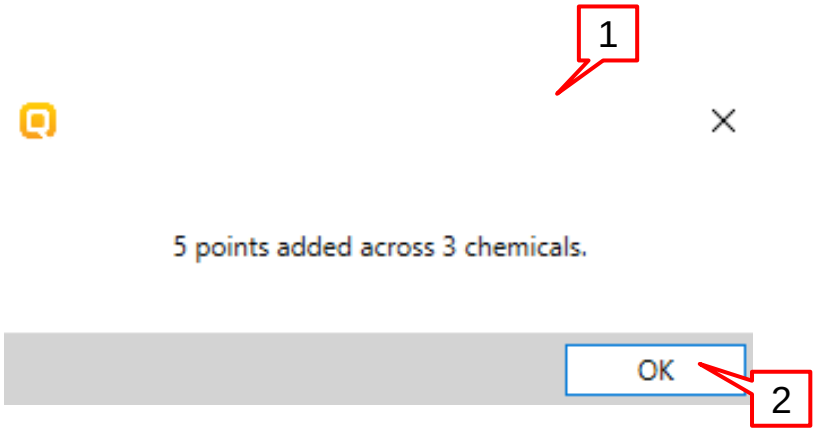
1. A message informing about the successful importing is shown, where you have to click on *OK* (1);
2. The 13 chemicals are loaded on the matrix (2).

Gathering of experimental data for skin sensitization



1. Go to *Data module* (1);
2. Select *Skin sensitization database* (2);
3. Click on *Gather* (3), and then click *OK* to collect the data for all endpoints (4)

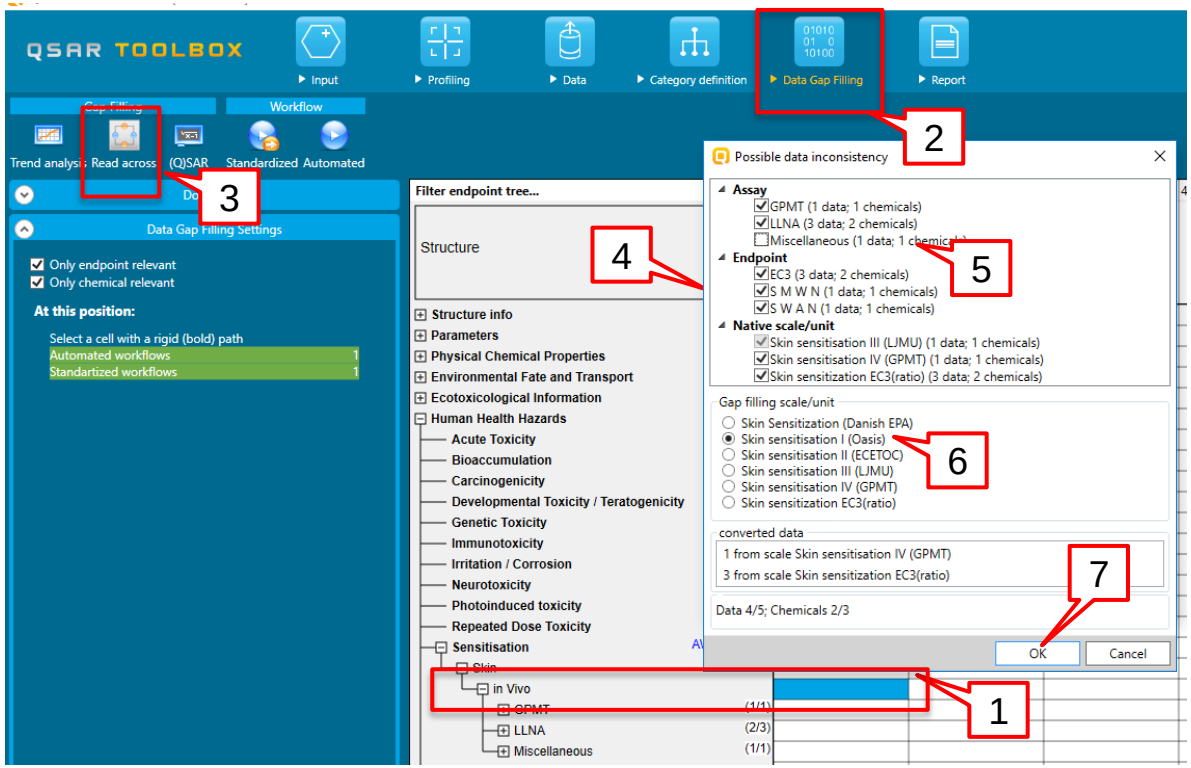
Gathering of experimental data for skin sensitization



1. An informative message appears (1)
2. Click *OK*(2);

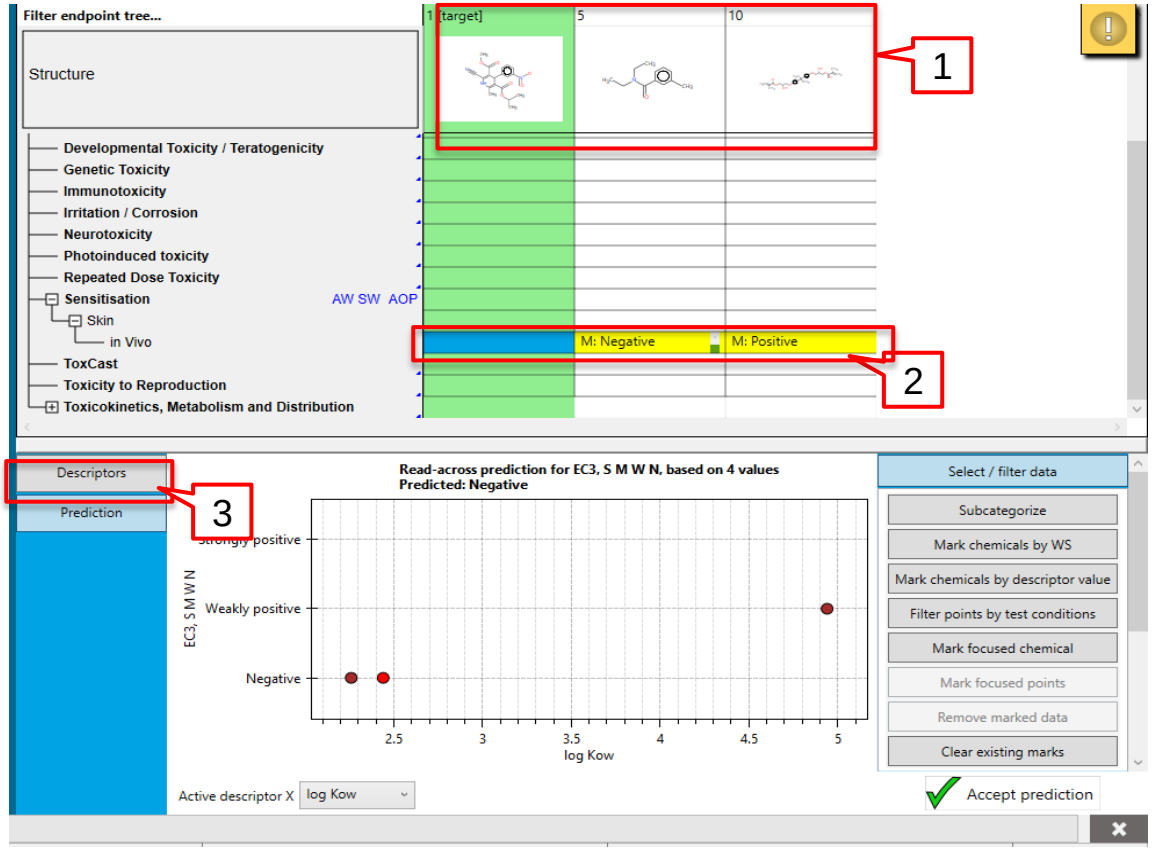
Data gap filling

1. Expand the endpoint tree and go to Sensitization/Skin/in Vivo (1);
2. Go to data gap filling module (2);
3. Click on *Read across* (3);
4. In *Possible data inconsistency window* (4) uncheck Miscellaneous (5) and select Skin sensitization I (OASIS)(6)
5. Click on *OK* (7).

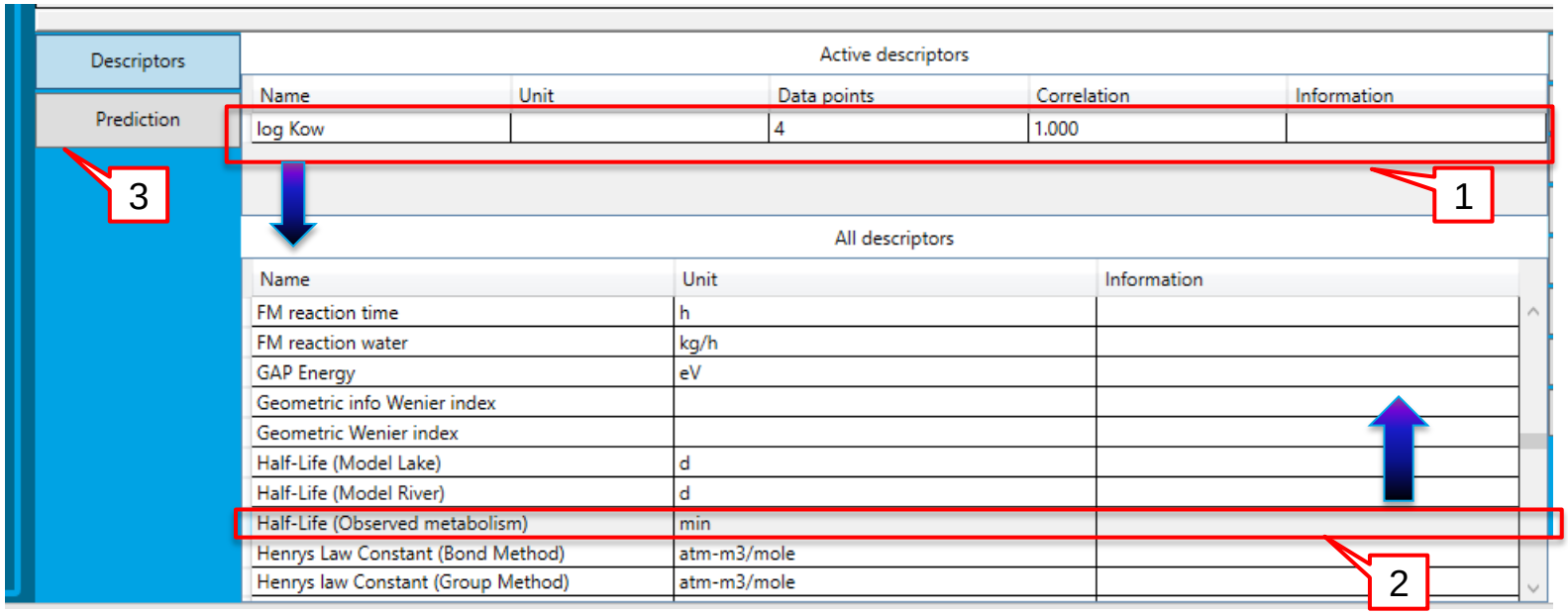


Data gap filling

1. Three chemicals are entered into the read-across.; one target and two analogues (1)
2. The experimental data is displayed on the matrix. (2)
3. Select Descriptors to change the descriptor on the x axis of the graph



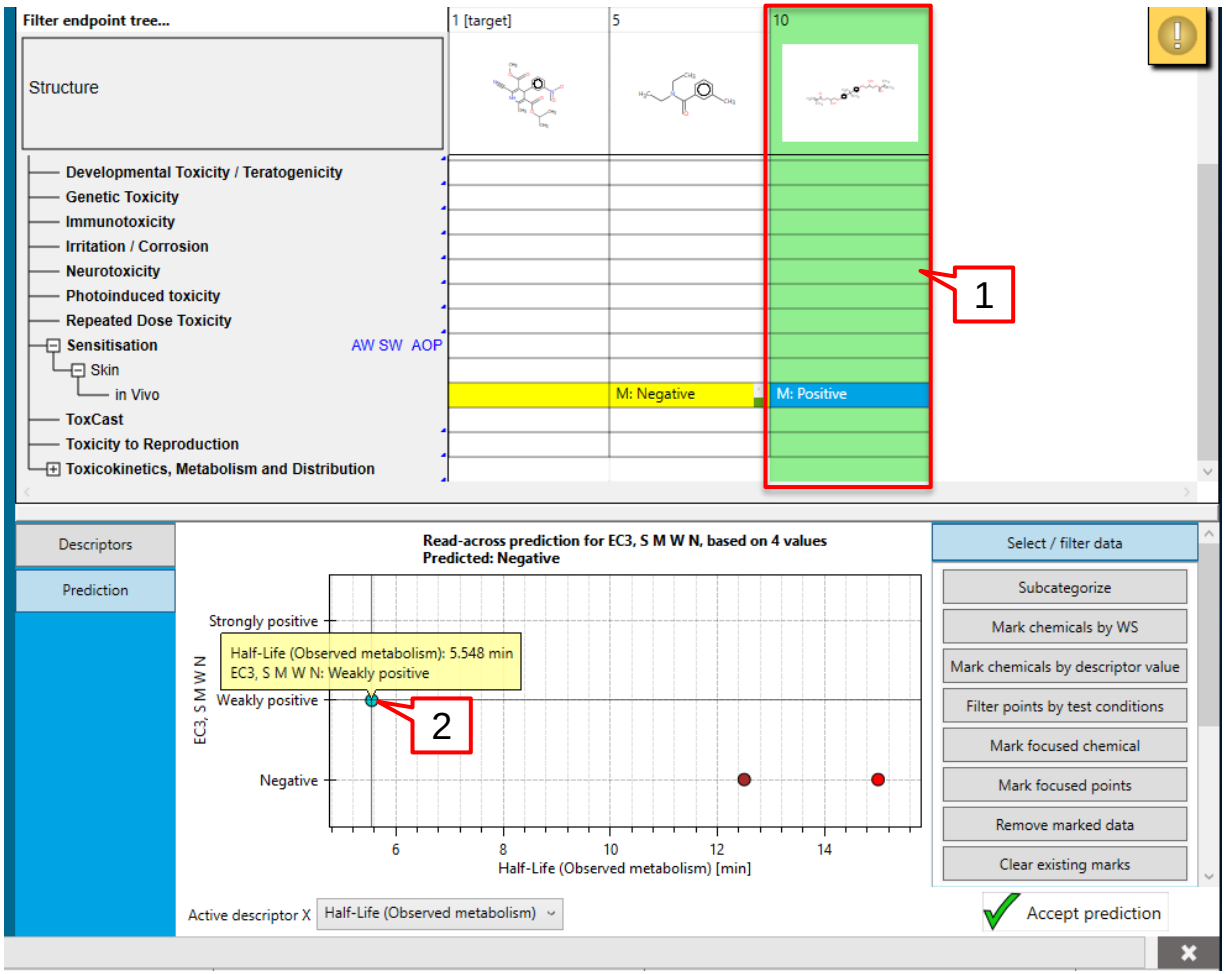
Data gap filling



1. Double left click on the *Active descriptor* LogKow (1) to shift it to the *All descriptors* list.
2. Then double left click on *Half-life (observed metabolism)* (2) to shift the descriptor to the *Active descriptors* panel, which makes it x-axis descriptor.
3. Click on *Prediction* button.

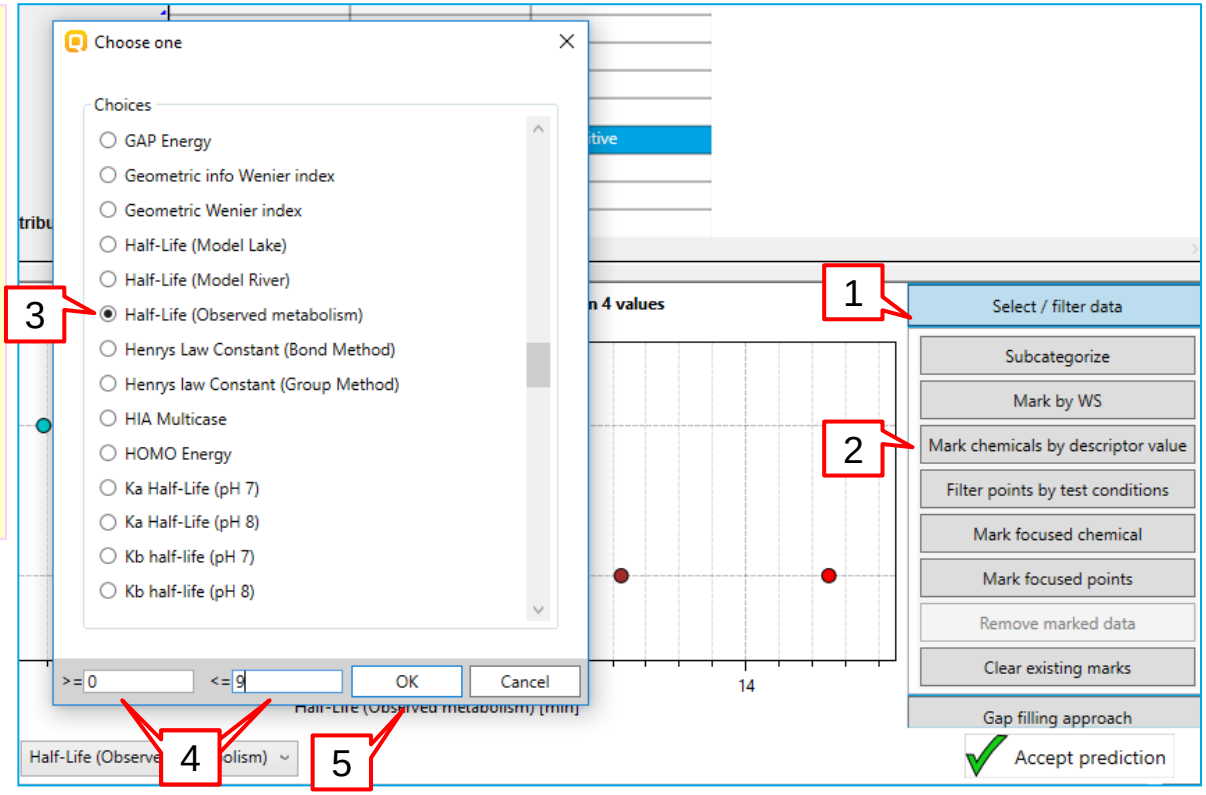
Data gap filling

As it can be seen the analogue with positive data (1) has very low half-life value (2).
Left click over the point and then hold it to see details (2). Based on the that, the chemical could be removed from the analysis (see next slide).

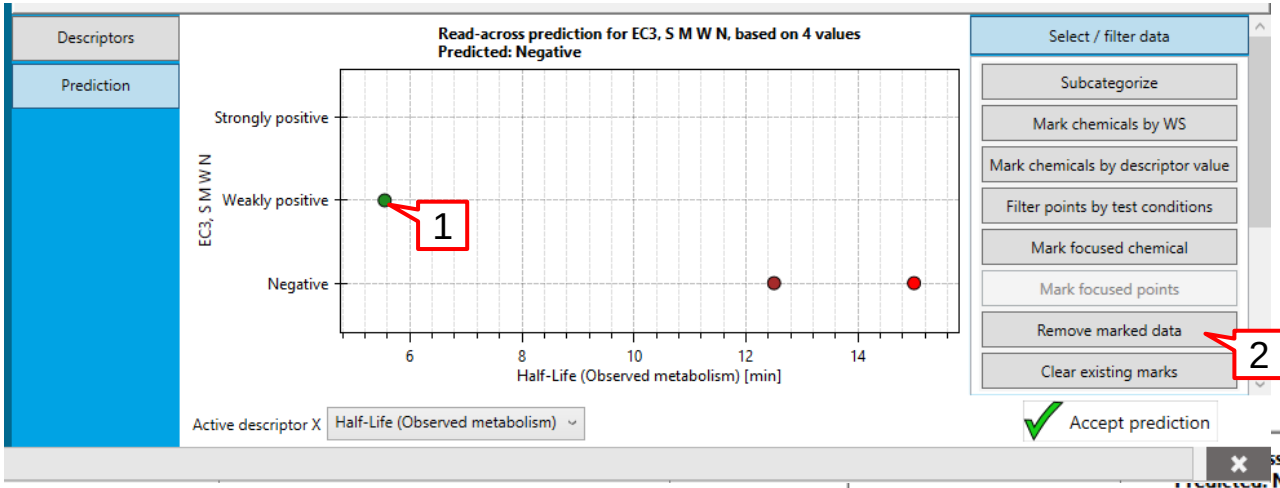


Data gap filling

1. Open *Select/filter data* (1).
2. Click on *Mark chemicals by descriptor value* (2).
3. Select *Half-life (observed metabolism)* (3).
4. Enter [0;9] range (4).
5. Click on *OK* (5).



Data gap filling



- Once the analogue is marked (1), click on *Remove marked data* (2) from the Select filter/data panel.
- Now the prediction is based only on the analogue with negative experimental data. (3)