

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

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

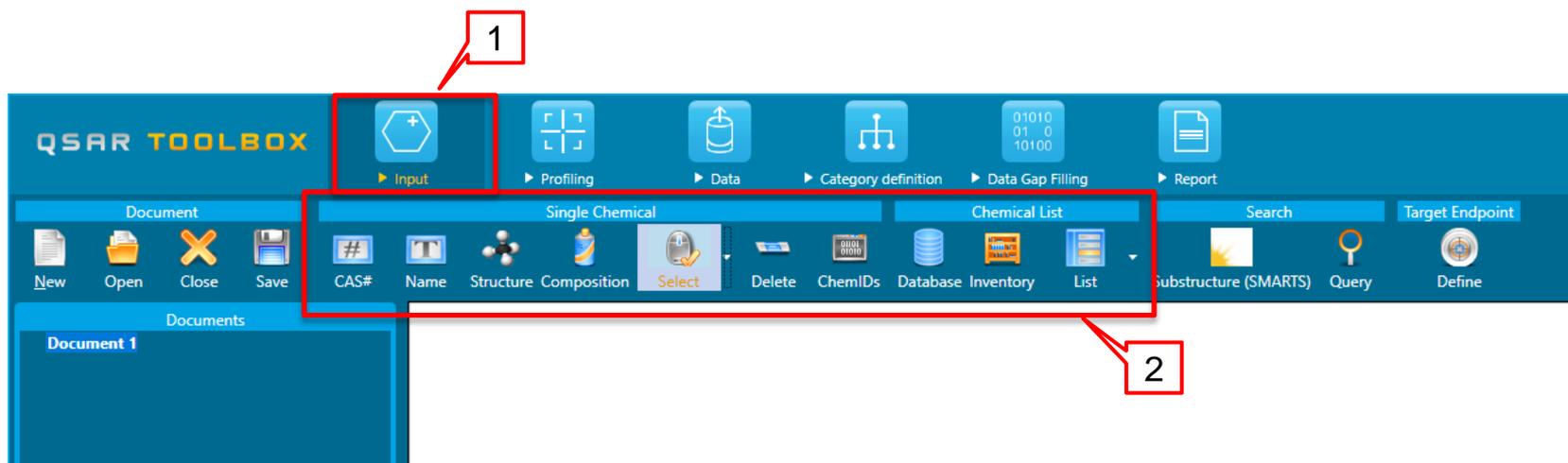
- Chemical Name
- Chemical Abstract Services (CAS) number (#)
- SMILES (simplified molecular information line entry system) notation
- Chemical with defined composition
- Drawing chemical structure
- Select from User List/Inventory/Databases

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).

The screenshot shows the QSAR Toolbox 4.0.0.26167 interface. The top toolbar contains icons for Input, Profiling (highlighted with a red box and '1'), Data, Category definition, and Data Gap Filling. Below the toolbar are buttons for Apply, View, New, and Delete. The 'Documents' panel shows 'Profiling methods' with a tree view where 'Observed rat liver metabolism with quantitative data' is checked (highlighted with a red box and '2'). The 'Apply' button is highlighted with a red box and '3'. The 'Filter endpoint tree...' panel shows a tree view where 'Metabolism/Transformations' is expanded, and 'Observed rat liver metabolism with quantitative data' is selected (highlighted with a red box and '4'). The results table on the right shows '1 [target]' and '2 metabolites'.

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).

The screenshot displays the QSAR Toolbox Profiling interface. On the left, there are two panels for selecting profiling methods. The top panel, 'Profiling methods', lists various endpoints such as DNA alerts, eye irritation, and mutagenicity. The bottom panel, 'Metabolism/Transformations', lists metabolic endpoints, with 'Observed rat liver metabolism with quantitative data' selected. On the right, the 'Filter endpoint tree...' panel shows a tree structure where 'Observed rat liver metabolism with quantitative data' is highlighted. A context menu is open over this item, with three red boxes and arrows indicating the steps: (1) right-clicking on the item, (2) selecting 'Observed rat liver metabolism with quantitative data', and (3) clicking on 'Show metabolic map'.

Profiling

[94.001.Liver] 134-62-3; N,N-Diethyl-m-toluamide; Rat
 Yeung, J. M., W. G. Taylor, Drug Metab. Dispos., 16(4), (1988). (in vitro), (p. 600 - 604)

- 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

2 [94.001.Liver 134-62-3; N,N-Diethyl-m-toluamide; Rat

Yeung, J. M., W. G. Taylor, Drug Metab. Dispos., 16(4), (1988). (in vitro), (p. 600 - 604) **3**

1

▼ Treatment group 1 Rat, male, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000 nmol, single dose (non-radiolabeled), Wistar

▲ Treatment group 2 Rat, female, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000 nmol, single dose (non-radiolabeled), Wistar

Study	Rat, female, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000 nmol, single dose (non-radiolabeled), Wistar
Citations	Yeung, J. M., W. G. Taylor, Drug Metab. Dispos., 16(4), (1988). (in vitro), (p. 600 - 604)
Subjects	Species - Rat Gender - Female (5 subjects) Weight - Between 210 - 225 g (female) Age - 12 weeks old Strain - Wistar Source - Charles River (St. Constant, Quebec, Canada) Housing - Polycarbonate metabolism cages Diet - Ad libitum (Purina lab. chow) Water - Ad libitum
Environmental conditions	Env. temperature - Between 18 - 22 °C Humidity - Between 50 - 60 % Photoperiod - 12-h light/dark cycle Acclim. period - 4 days
In vivo / in vitro	In vitro Phase I enzymes - Detected (looked for and found) Phase II enzymes - Not determined (not looked for) Experimental system - Microsomes Organ / Tissue - Liver In vitro temperature - 37 °C

4

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

1

QTY

1.14.14.1

1.14.14.1

QTY

QTY

2

Treatment group 1 Rat, male, in vitro, Microsomes, liver, incubation media, in vitro

Study Rat, male, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000

Citations Yeung, J. M., W. G. Taylor, Drug Metab. Dispos., 16(4), (1988). (in vitro), (p.

Subjects Species - Rat
Gender - Male (5 subjects)
Weight - Between 275 - 300 g (male)
Age - 12 weeks old
Strain - Wistar
Source - Charles River (St. Constant, Quebec, Canada)
Housing - Polycarbonate metabolism cages
Diet - Ad libitum (Purina lab. chow)
Water - Ad libitum

Environmental co... Env. temperature - Between 18 - 22 °C
Humidity - Between 50 - 60 %
Photoperiod - 12-h light/dark cycle
Acclim. period - 4 days

In vivo / in vitro In vitro
Phase I enzymes - Detected (looked for and found)
Phase II enzymes - Not determined (not looked for)
Experimental system - Microsomes
Organ / Tissue - Liver
In vitro temperature - 37 °C
Exper. descriptors - Not reported

Sampling / anal... Sample matrix - Incubation media
Sample times (frequency) - Minutely
Duration - 120 minutes
Amount - 500 microl
Separations - High-performance liquid chromatography (HPLC)
Detections - Ultraviolet spectroscopy (UV)
Extraction methods - Solvent (acetonitrile)
Conj. analysis methods - Not reported

Dose administra... Administration type - In vitro incubation
Dosing (non-radiolabeled parent) - 1000 nmol, single dose

Additional infor... Microsomes from male rats metabolized DEET much faster than did those from fe

Quantity of metabolite as function of time

Time, min	0.00	5.00	10.0	15.0	20.0	30.0	40.0	60.0	90.0
Quantity, nmol	1E3	718	588	518	471	423	400	365	329

- 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

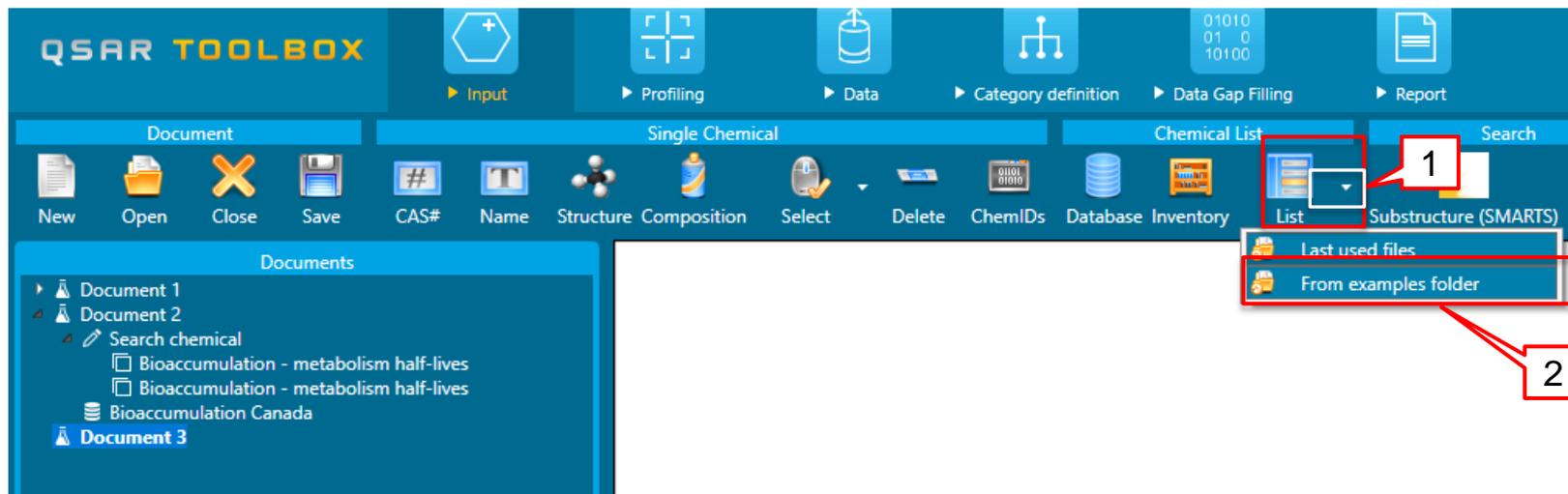
An overview

- 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 quantitative metabolic data in data gap filling

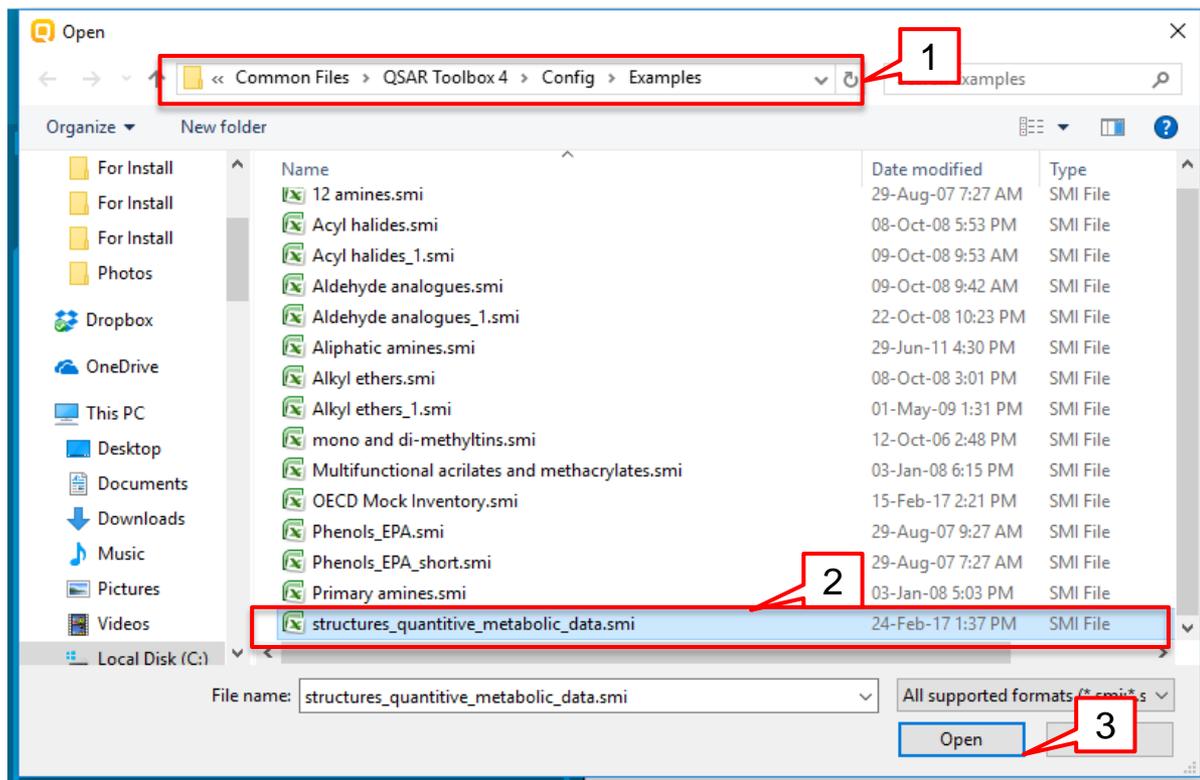
- Quantitative metabolic data could be used to filter analogues in data gap filling.
- Quantities cannot be used directly to filter out chemicals (quantities are not single values, but time series; often data comes in units, which are not convertible - i.e. mol/L vs mol/g protein).
- In this respect 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



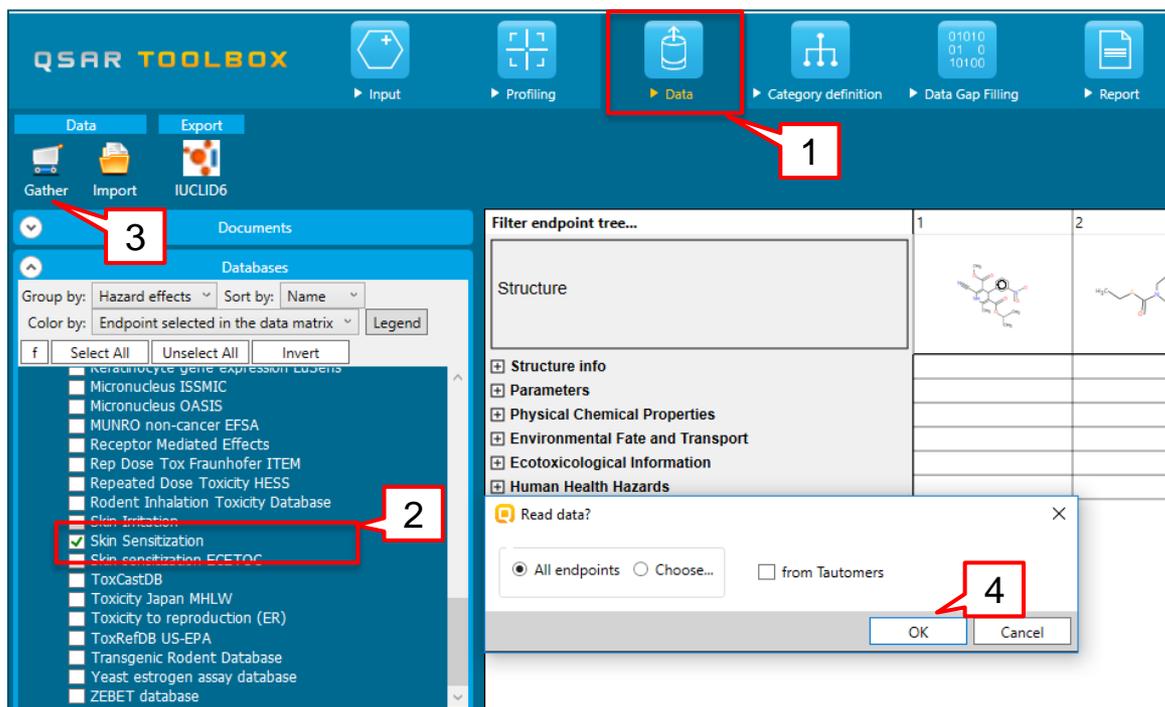
1. Examples folder directory in Toolbox is open (1);
2. Select *structure_quantitive_metabolic_data.smi*(2);
3. Click on Open (3)

Input list of chemicals

The screenshot displays the QSAR Toolbox 4.0.0.26167 interface. The top menu bar includes options like Document, Single Chemical, Chemical List, Search, and Target Endpoint. Below this is a toolbar with icons for New, Open, Close, Save, CAS#, Name, Structure, Composition, Select, Delete, ChemIDs, Database, Inventory, List, Substructure (SMARTS), Query, and Define. On the left, a 'Documents' panel shows a tree view with folders for Document 1, Document 2, and Document 3, containing sub-items like 'Search chemical' and 'structures_quantitative_metabolic_data'. The main workspace is divided into a 'Filter endpoint tree...' on the left and a matrix on the right. The matrix has 6 columns and several rows. The first row is labeled 'Structure' and contains chemical structures in columns 1 through 5. A 'Success' dialog box is overlaid on the matrix, displaying the message '13 structure(s) were successfully imported.' and an 'OK' button. Two red callout boxes with numbers '1' and '2' point to the 'OK' button and a cell in the matrix, respectively.

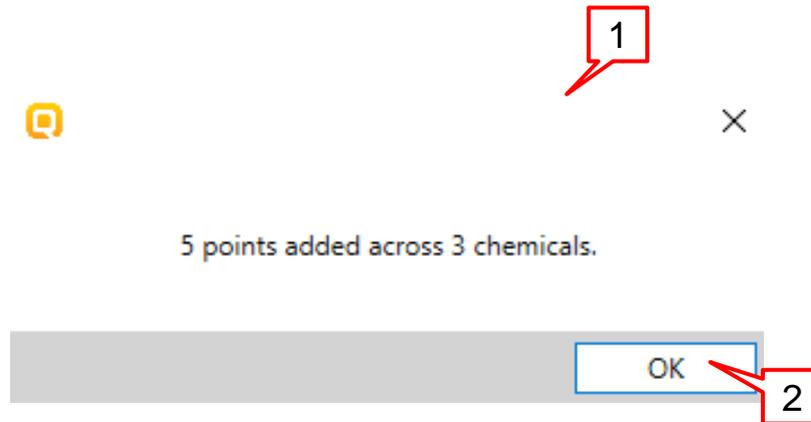
1. A message informing about the successful importing is shown, where you have to click on OK (1);
2. The 13 chemicals are loaded on the matrix (2).

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).

The screenshot shows the QSAR Toolbox interface with the 'Data Gap Filling' module selected in the top navigation bar. A 'Possible data inconsistency' dialog box is open, displaying a list of assays and endpoints. The 'Miscellaneous' checkbox is unchecked, and 'Skin sensitisation I (OASIS)' is selected under the 'Gap filling scale/unit' section. The 'Data 4/5; Chemicals 2/3' summary is visible at the bottom of the dialog. The 'Filter endpoint tree...' panel on the left shows the 'in Vivo' endpoint expanded under 'Skin'.

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 (3)

The screenshot displays the QSAR Toolbox interface. On the left, a 'Filter endpoint tree...' lists various toxicity endpoints. The main area shows a matrix with three columns for chemicals and rows for endpoints. A red box labeled '1' highlights the chemical structures in the top row. Below the matrix, a red box labeled '2' highlights the 'M: Negative' and 'M: Positive' data points. At the bottom, a red box labeled '3' highlights the 'Descriptors' dropdown menu. To the right of the matrix is a 'Read-across prediction for EC3, S M W N, based on 4 values' graph. The graph shows three data points: two 'Negative' points at low log Kow values and one 'Weakly positive' point at a high log Kow value. A 'Select / filter data' panel is visible on the right, and an 'Accept prediction' button is at the bottom right.

Data gap filling

Descriptors		Active descriptors			
	Name	Unit	Data points	Correlation	Information
Prediction	log Kow		4	1.000	

All descriptors		
Name	Unit	Information
FM reaction time	h	
FM reaction water	kg/h	
GAP Energy	eV	
Geometric info Wenier index		
Geometric Wenier index		
Half-Life (Model Lake)	d	
Half-Life (Model River)	d	
Half-Life (Observed metabolism)	min	
Henrys Law Constant (Bond Method)	atm-m3/mole	
Henrys law Constant (Group Method)	atm-m3/mole	

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 that, the chemical could be removed from the analysis (see next slide).

The screenshot displays the QSAR Toolbox interface. On the left, a 'Filter endpoint tree...' is visible with categories like 'Developmental Toxicity / Teratogenicity', 'Genetic Toxicity', 'Immunotoxicity', 'Irritation / Corrosion', 'Neurotoxicity', 'Photoinduced toxicity', 'Repeated Dose Toxicity', 'Sensitisation', 'Skin', 'in Vivo', 'ToxCast', 'Toxicity to Reproduction', and 'Toxicokinetics, Metabolism and Distribution'. The 'Sensitisation' category is expanded to show 'Skin' and 'in Vivo'. The 'in Vivo' sub-category is selected, and the 'AW SW AOP' filter is applied.

In the center, a table shows data for three chemical structures. The first structure is highlighted with a red box and labeled '1'. The second structure is also highlighted with a red box and labeled '2'. The third structure is highlighted with a red box and labeled '10'. The table has columns for '1 [target]', '5', and '10'. The 'M: Negative' and 'M: Positive' rows are highlighted in yellow and blue respectively.

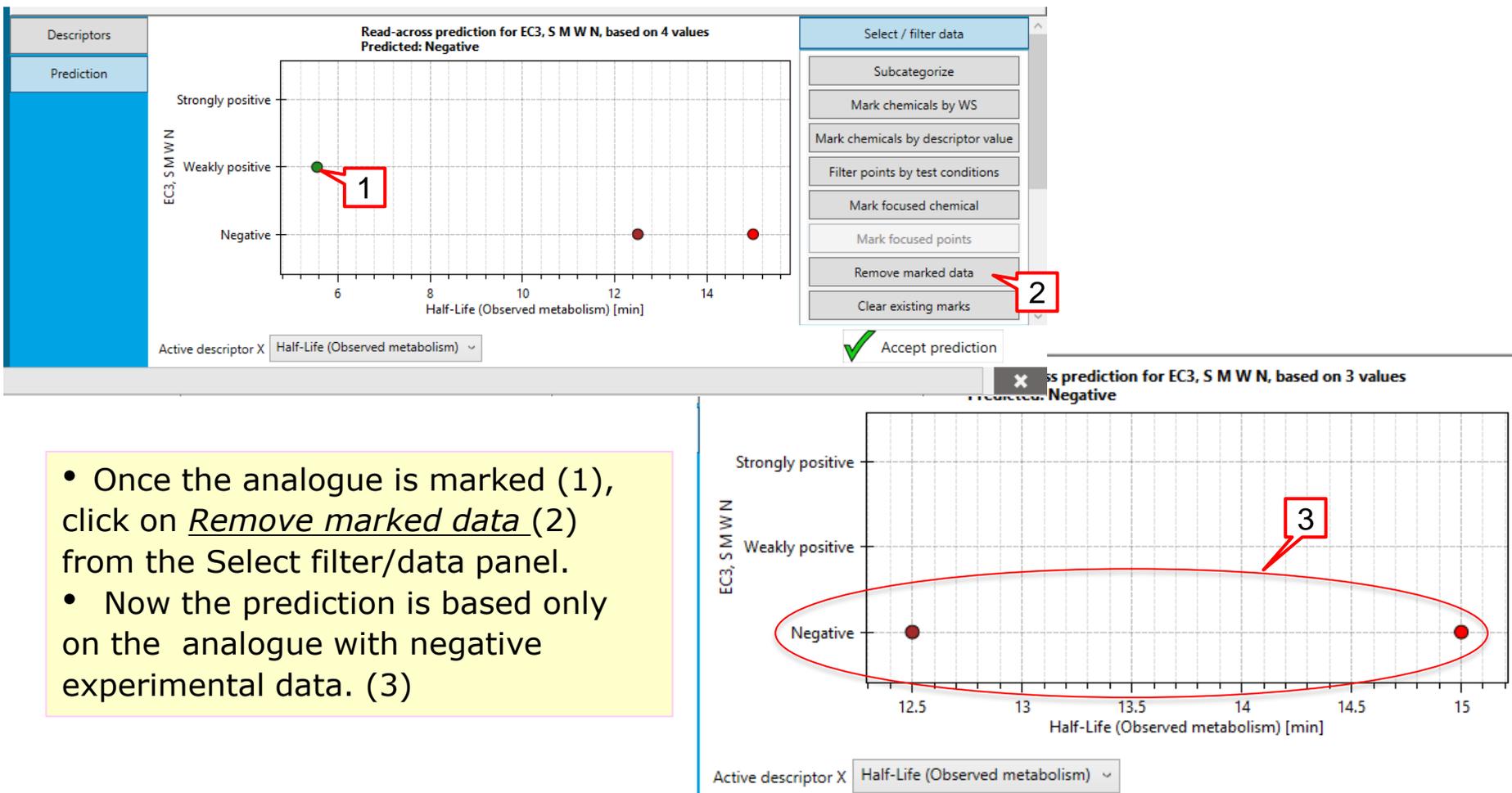
At the bottom, a scatter plot titled 'Read-across prediction for EC3, S M W N, based on 4 values Predicted: Negative' is shown. The y-axis is 'EC3, S M W N' with categories 'Strongly positive', 'Weakly positive', and 'Negative'. The x-axis is 'Half-Life (Observed metabolism) [min]' with values 6, 8, 10, 12, 14. A point is highlighted with a red box and labeled '2', with a callout box showing 'Half-Life (Observed metabolism): 5.548 min' and 'EC3, S M W N: Weakly positive'. Other points are shown at approximately (12.5, Negative) and (15, Negative). A 'Select / filter data' panel on the right contains buttons for 'Subcategorize', 'Mark chemicals by WS', 'Mark chemicals by descriptor value', 'Filter points by test conditions', 'Mark focused chemical', 'Mark focused points', 'Remove marked data', and 'Clear existing marks'. A 'Accept prediction' button with a green checkmark is at the bottom right.

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).

The screenshot displays the 'Choose one' dialog box in the foreground, which is used to select a descriptor for data gap filling. The dialog lists various descriptors, with 'Half-Life (Observed metabolism)' selected. Below the list, there are input fields for a range: '>= 0' and '<= 9'. The 'OK' button is highlighted. In the background, the main software interface is visible, showing a plot with two data points and a menu on the right. The 'Select / filter data' button is highlighted in the menu, and the 'Mark chemicals by descriptor value' option is also highlighted. A 'Gap filling approach' section at the bottom right shows a checked box for 'Accept prediction'.

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)