QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

OECD (Q)SAR Toolbox v.4.4.1

Step-by-step example for predicting skin sensitization accounting for the abiotic activation of the chemicals

Outlook

- **Background**
- Keywords
- Objectives
- The exercise
- Workflow
- Save/Load

Background

- This is a step-by-step presentation designed to take the user through the Toolbox workflow for predicting skin sensitization potential of a target chemical taking into account its abiotic activation.

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Keywords

TARGET CHEMICAL - chemical of interest

MODULE – a Toolbox module is a section dedicated to specific actions and options (e.g. Profiling)

WORKFLOW – the use, in combination, of the different modules (e.g. prediction workflow: from input to report)

PROFILER - algorithm (rule set) for the identification of specific features of the chemicals. Several types of profilers are available, such as structural (e.g. Organic functional groups), mechanistic (e.g. Protein binding by OECD) and endpoint-specific (e.g. in vitro in vitro mutagenicity (Ames test) alerts by ISS) profilers.

ALERT - the profilers consist of sets of rules or alerts. Each of the rules consists of a set of queries. The queries could be related to the chemical structure, physicochemical properties, experimental data, comparison with the target or list with substances and external queries from other predefined profilers (reference queries).

CATEGORY – "group" of substances sharing same characteristics (e.g. the same functional groups or mode of action). In a typical Toolbox workflow, it consists of the target chemical and its analogues gathered according to the selected profilers

ENDPOINT TREE – Endpoints are structured in a branched scheme, from a broader level (Phys-Chem properties, Environmental Fate and transport, Ecotoxicology, Human health hazard) to a more detailed one (e.g. EC3 in LLNA test under Human health hazard-Skin sensitization)

DATA MATRIX – Table reporting the chemical(s) and data (experimental results, profilers outcomes, predictions). Each chemical is in a different column and each data in a different row

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Objectives

This presentation demonstrates a number of functionalities of Toolbox 4.4:

- Define the target chemical and the target endpoint.
- Profiling the target chemical.
- Identifying analogues of the target chemical.
- Filling data gaps of the target chemical by read-across.
- Profiling the target chemical taking into account its (a)biotic activation.
- Identifying analogues of the target based on its (a)biotic activation
- Filling data gaps of the target chemical by read-across when the (a)biotic activation is taken into account.

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The Exercise

- In this exercise our target chemical will be **Eugenol [CAS# 97-53-0].**
- We will predict the Skin sensitization potential of Eugenol.
- Two types of categorization will be applied:
  - Identifying analogues by using well-known categorization group.
  - Identifying analogues based on the autoxidation activation of the target.

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Workflow

- **As you know the Toolbox has 6 modules which are typically used in sequence:**
  - Chemical Input
  - Profiling
  - Data
  - Categorization
  - Data Gap Filling
  - Report
- **In this example we will use the modules in a different order, tailored to the aims of the example.**

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - **Input**
    - **Input chemical by CAS#**
    - **Define target endpoint**

Input
Overview

- This module provides the user with several means of entering the chemical of interest (i.e. 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.

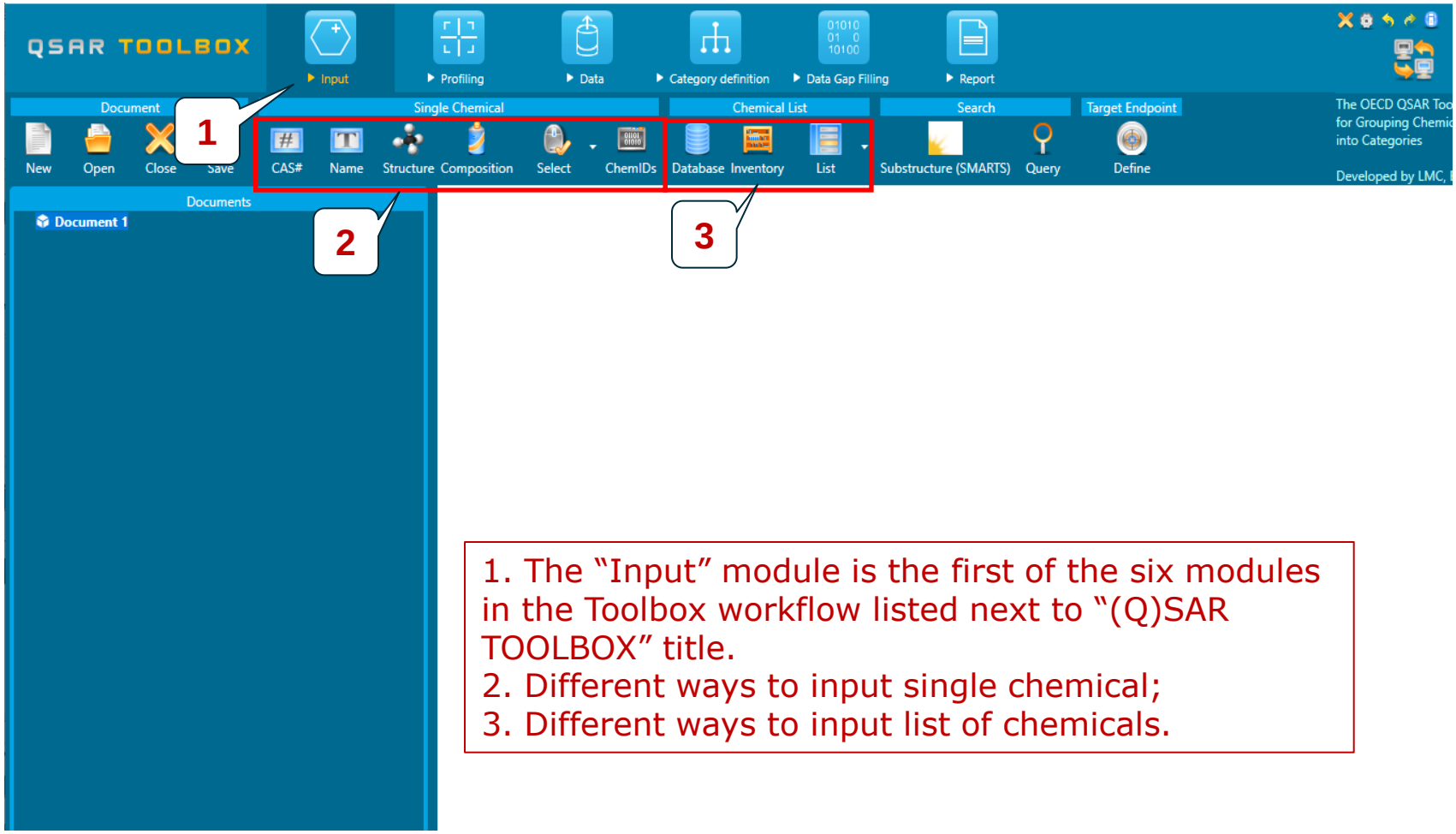
Input
Input chemical(s)

Alternative ways to input chemical(s):

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

B. Group of chemicals
- User List/Inventory
- Specialized Databases

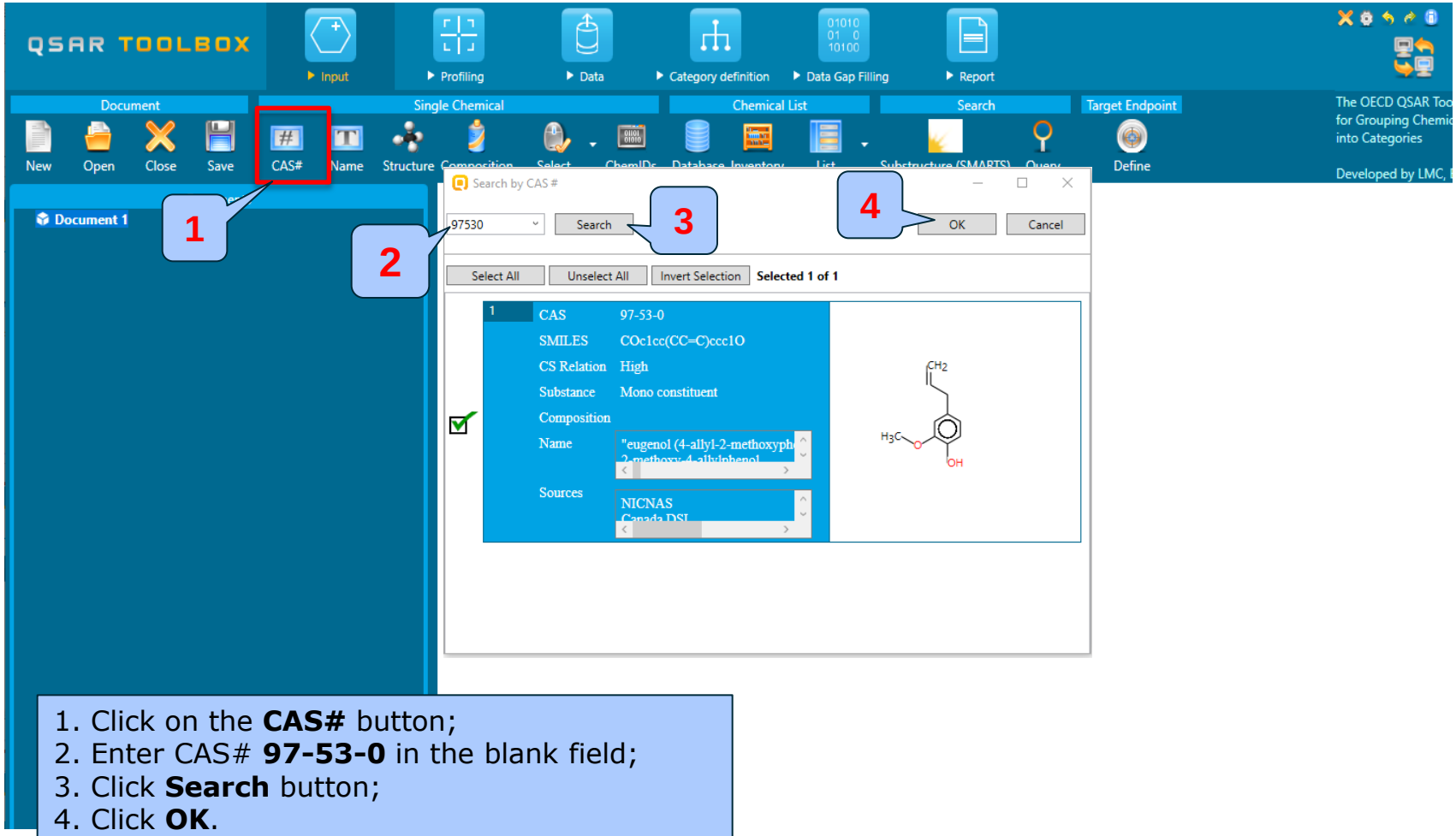
Input
Input Screen



1. The "Input" module is the first of the six modules in the Toolbox workflow listed next to "(Q)SAR TOOLBOX" title.
2. Different ways to input single chemical;
3. Different ways to input list of chemicals.

Input

Input target chemical by CAS#

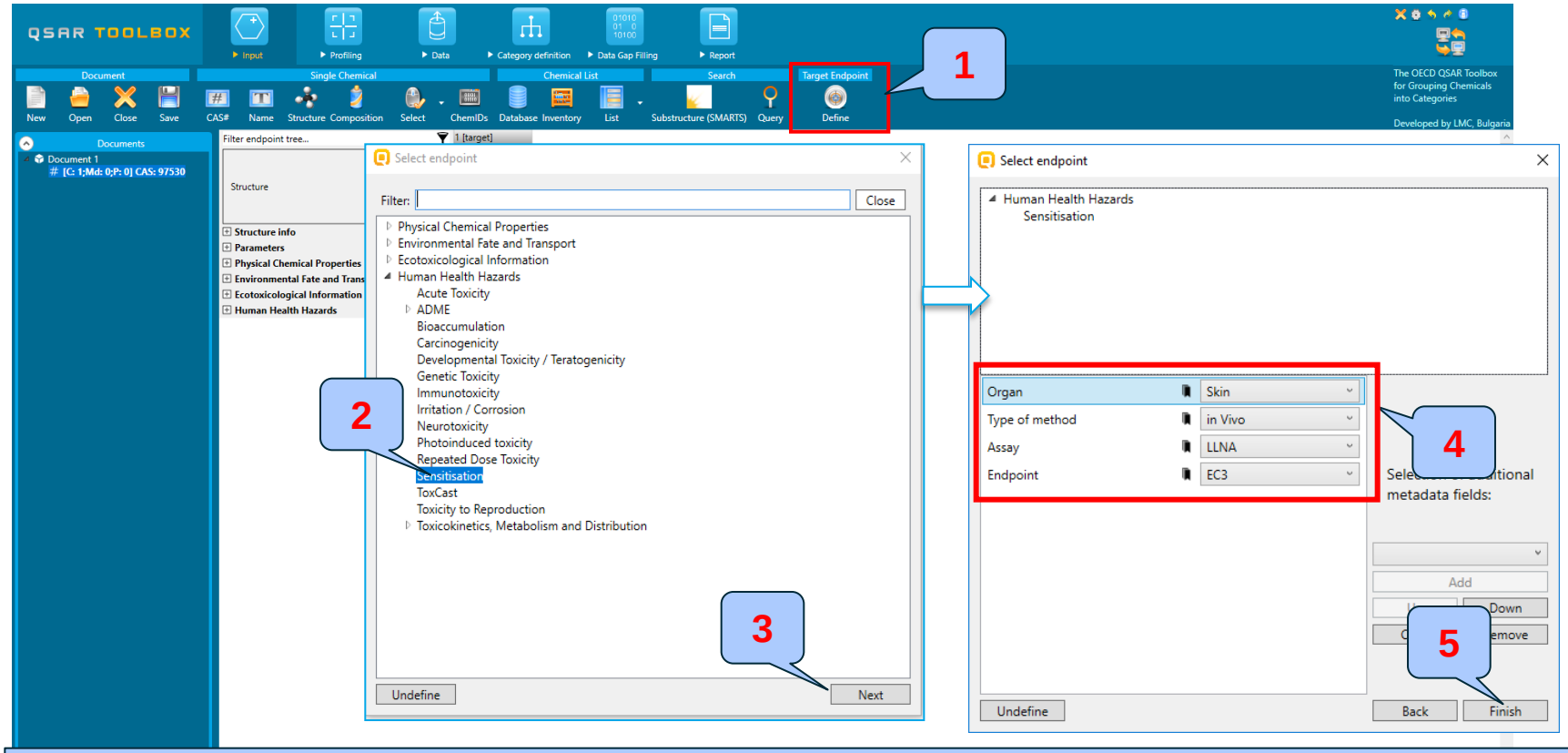


1. Click on the **CAS#** button;
2. Enter CAS# **97-53-0** in the blank field;
3. Click **Search** button;
4. Click **OK**.

Input
Define target endpoint - overview

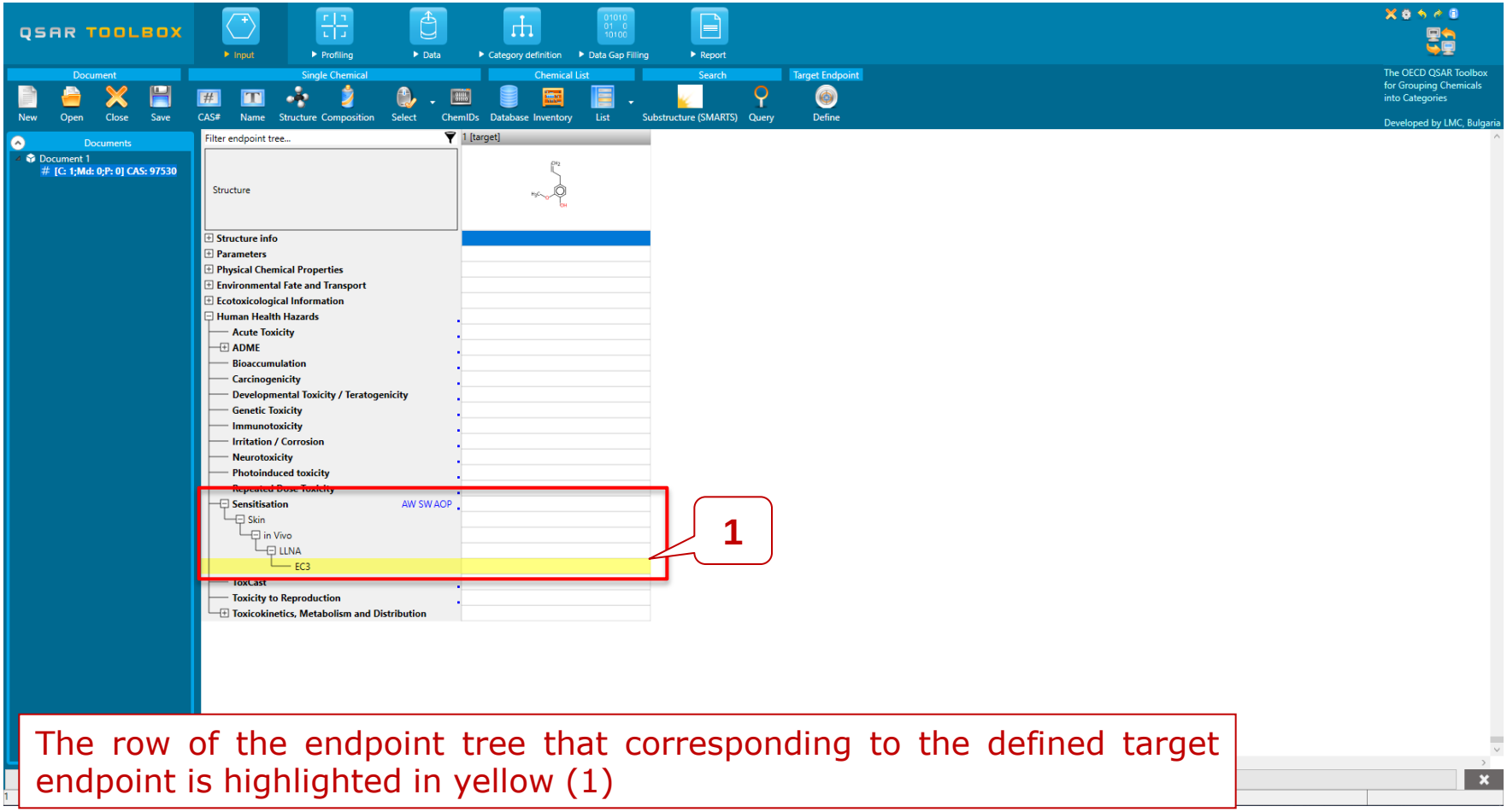
- The Define target endpoint functionality allows entering the endpoint of interest e.g., EC3, LC50, gene mutation etc.
- The relevant profiles and databases are become highlighted in color once the targeted endpoint is preliminary defined by this functionality (in green – the most suitable, in orange – the plausible);
- Calculation of alert performance (AP) is only possible if the target endpoint is preliminary defined (will be shown later on);
- There are different ways for defining the target endpoint (via the button from the Input module or by right click from the endpoint tree). For more details press F1 button in order to see the online help.

Input
Define target endpoint



Click on the **Define** button (1). In the new window select the general endpoint "*Sensitization*" (2) and click on **Next** (3).
Specify the endpoint using the drop-down menus as follows: For *Endpoint* select **EC3**; for *Assay* – **LLNA**; for *Type of method* - **in Vivo**; for *Organ* - "**Skin**" (4). Finally click on **Finish** (5).

Input
Define target endpoint



The row of the endpoint tree that corresponding to the defined target endpoint is highlighted in yellow (1)

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - **Profiling**

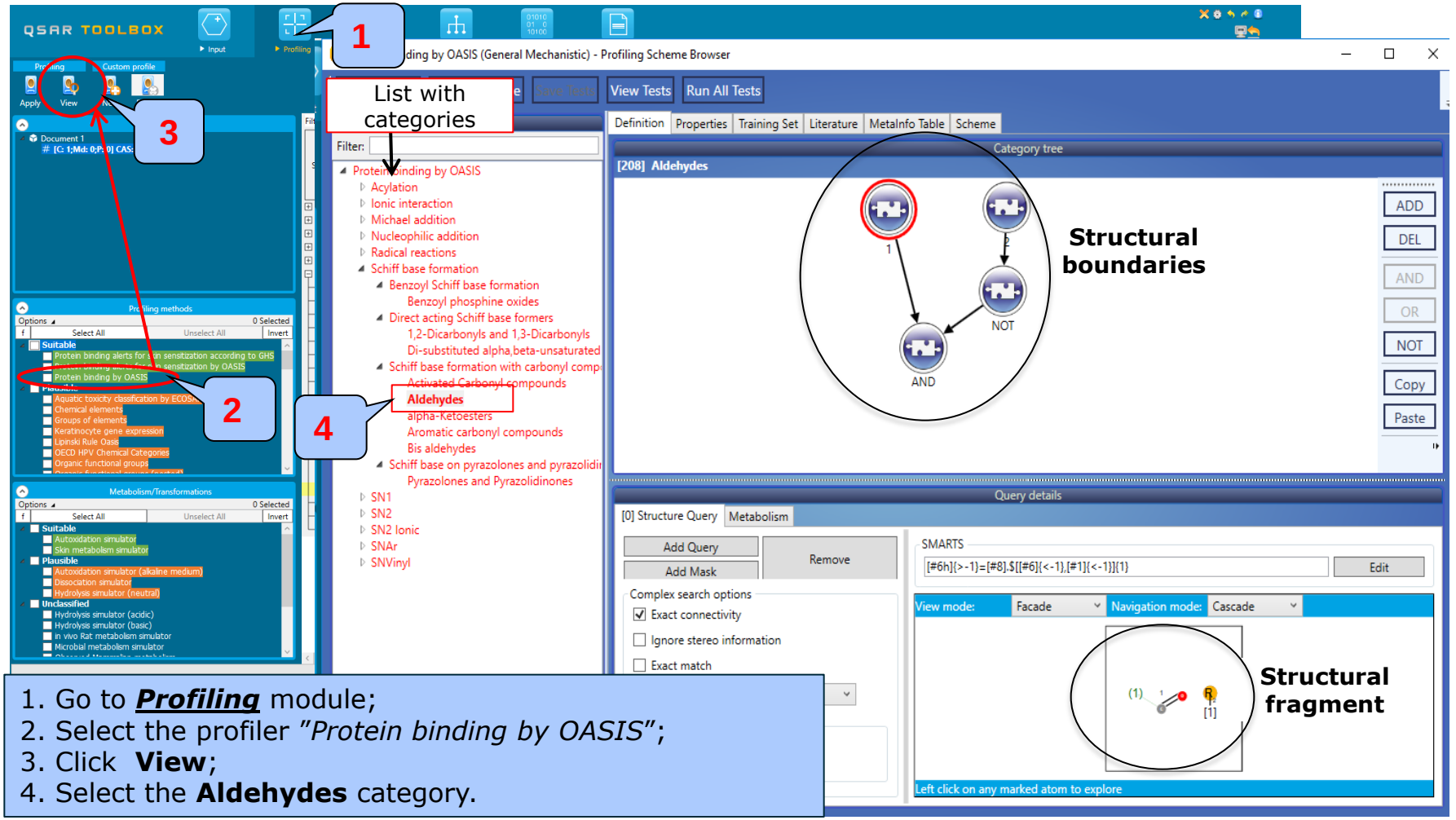
Profiling
Overview

- "Profiling" module contains all the knowledge in the system coded in profiling schemes (profilers);
- "Profilers" are a collection of empirical and mechanism knowledge (expertly derived) which could be used to analyse the structural properties of chemicals;
- The "profilers" identify the affiliation of the target chemical(s) to preliminary defined categories (functional groups/alerts);
- The "Profiling" module contains also observed and simulated metabolisms/transformations, which could be used in combination with the profiling schemes;
- The outcome of the profiling determines the most appropriate way to search for analogues, but they are also useful for preliminary screening or prioritization of substances;
- The "profilers" are not (Q)SARs, i.e. they are not prediction models themselves;
- Based on the "profilers' relevancy" (determined by the defined target endpoint), the most suitable once are getting colour highlighted*
- For most of the profilers, background information can be retrieved by selection of a profilers (for example, Protein binding by OASIS) and then click on "View'' (see the next slide).

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

Profiling

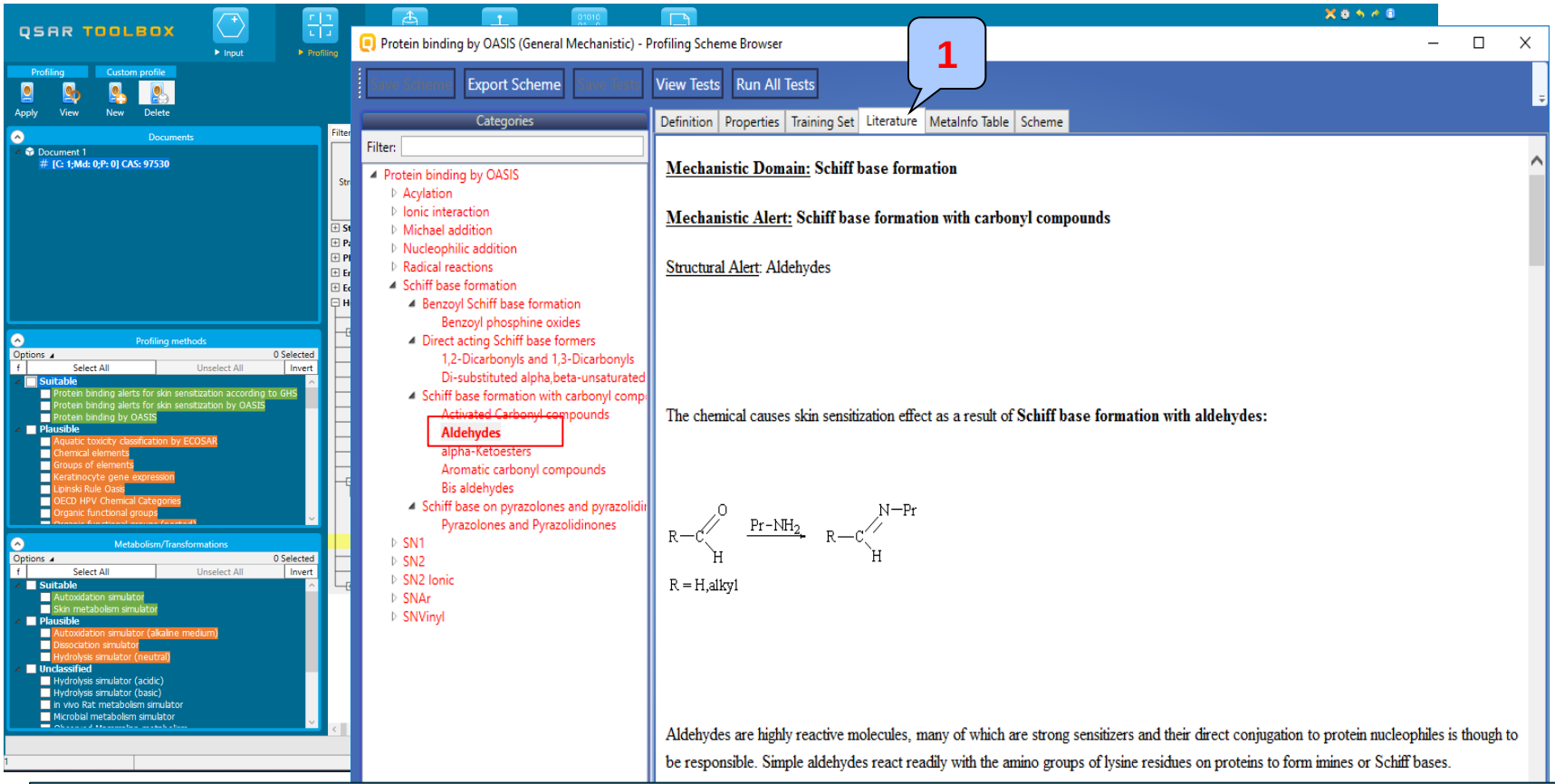
Profilers` background information



1. Go to ***Profiling*** module;
2. Select the profiler "*Protein binding by OASIS*";
3. Click **View**;
4. Select the **Aldehydes** category.

Profiling

Profilers` background information

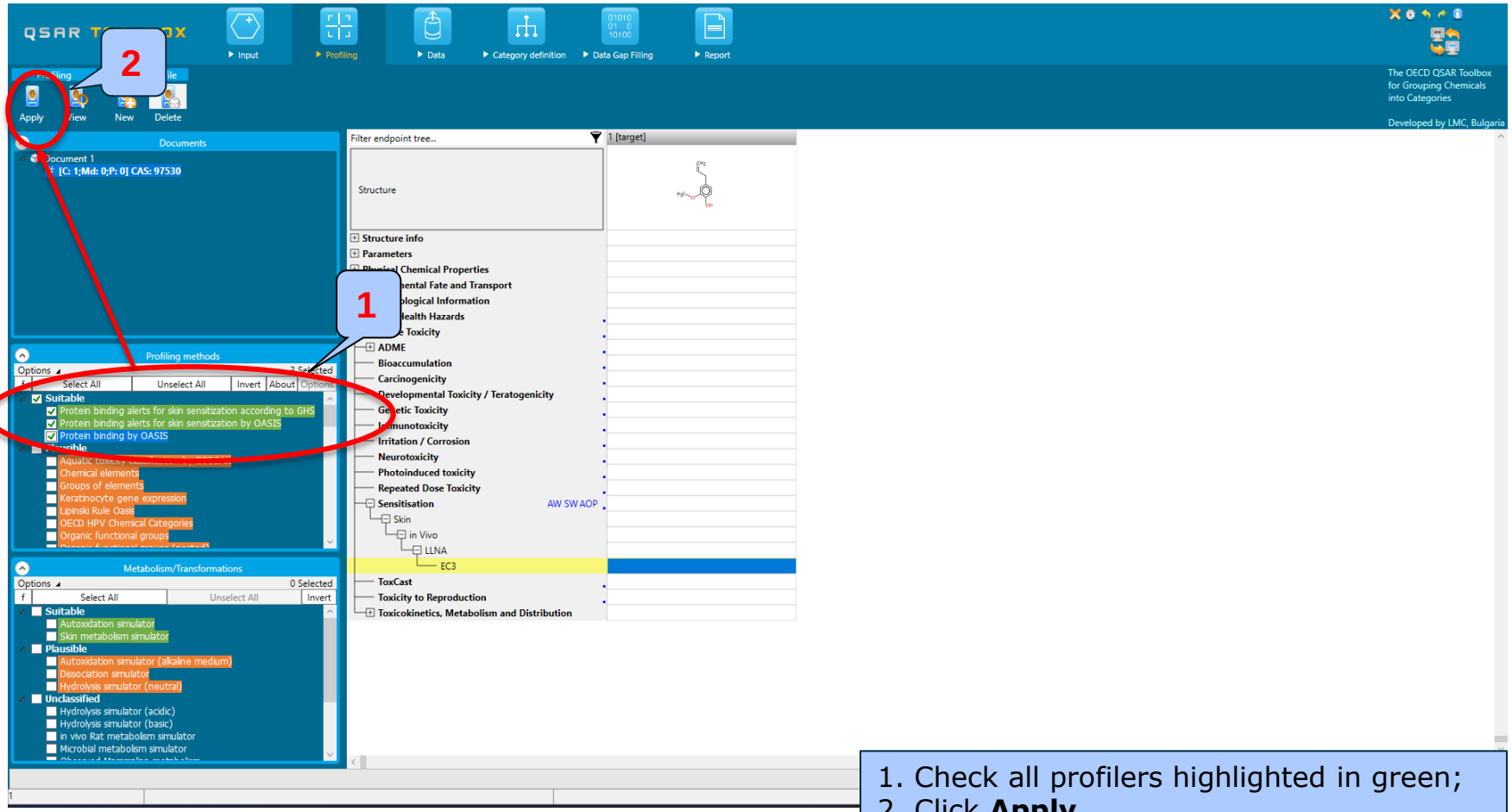


1. Go to the **Literature** tab in order to see detailed description of highlighted category (in this case "*Aldehydes*")

Profiling
Profiling the target chemical

- The outcome of the profiling determines the most appropriate way to search for analogues
- An option for coloring the profilers related to a given endpoint is implemented.
- The following profiling schemes are defined as relevant to the **Skin sensitization**:
  - *Protein binding by OASIS* – general mechanistic
  - *Protein binding alerts for skin sensitization according to GHS* – endpoint specific
  - *Protein binding alerts for skin sensitization by OASIS* - endpoint specific

Profiling
Profiling the target chemical



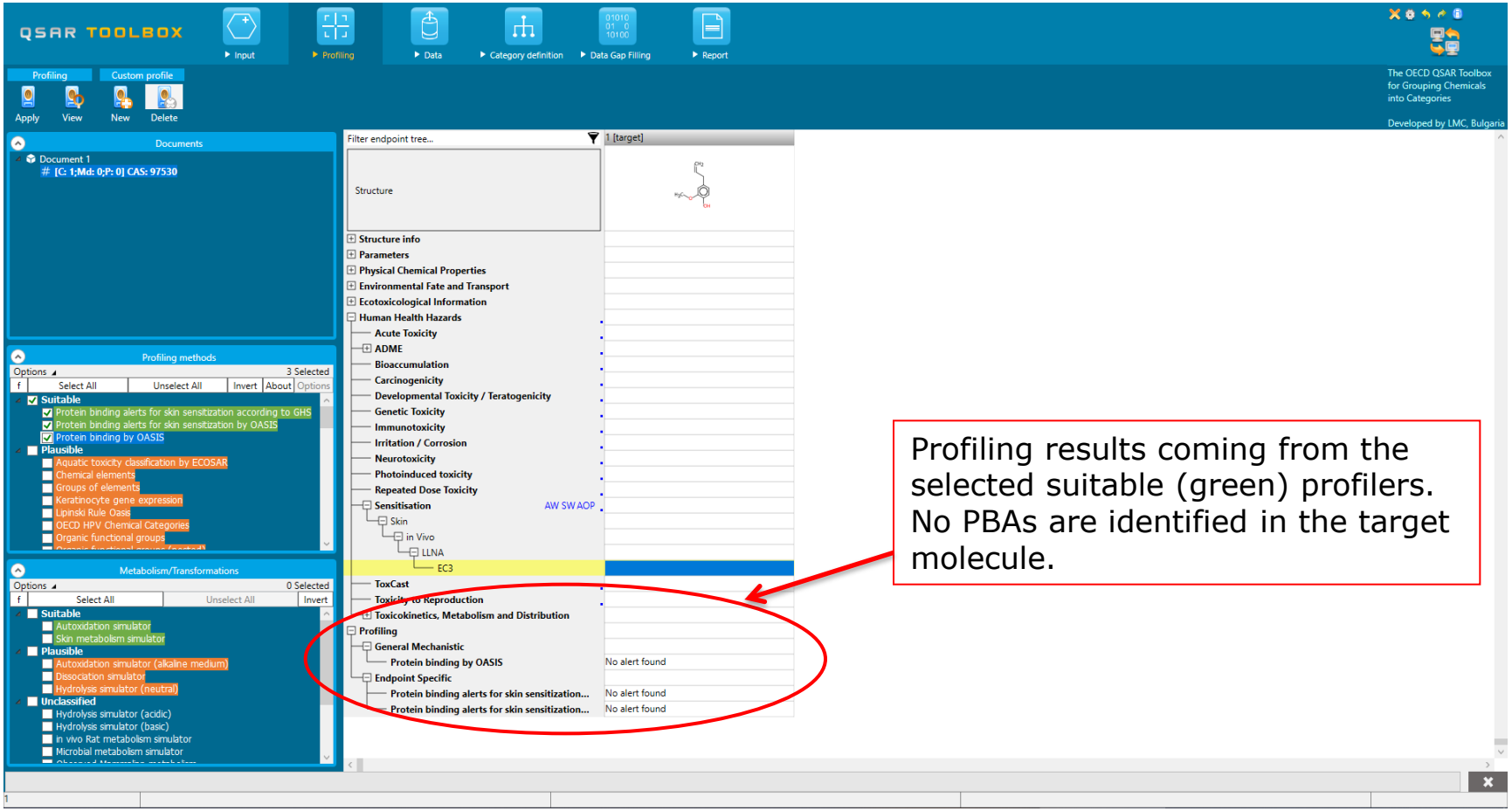
1. Check all profilers highlighted in green;
2. Click **Apply**.

Profiling
Profiling the target chemical

- The actual profiling will take up to several seconds depending on the number and type of profilers selected.
- The profiling result automatically appear as a last level of the endpoint tree (see next screenshot).
- In this case no protein binding alert (PBA) has been identified in the target substance (eugenol).

Profiling

Profiling the target chemical



Profiling results coming from the selected suitable (green) profilers. No PBAs are identified in the target molecule.

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - **Data**

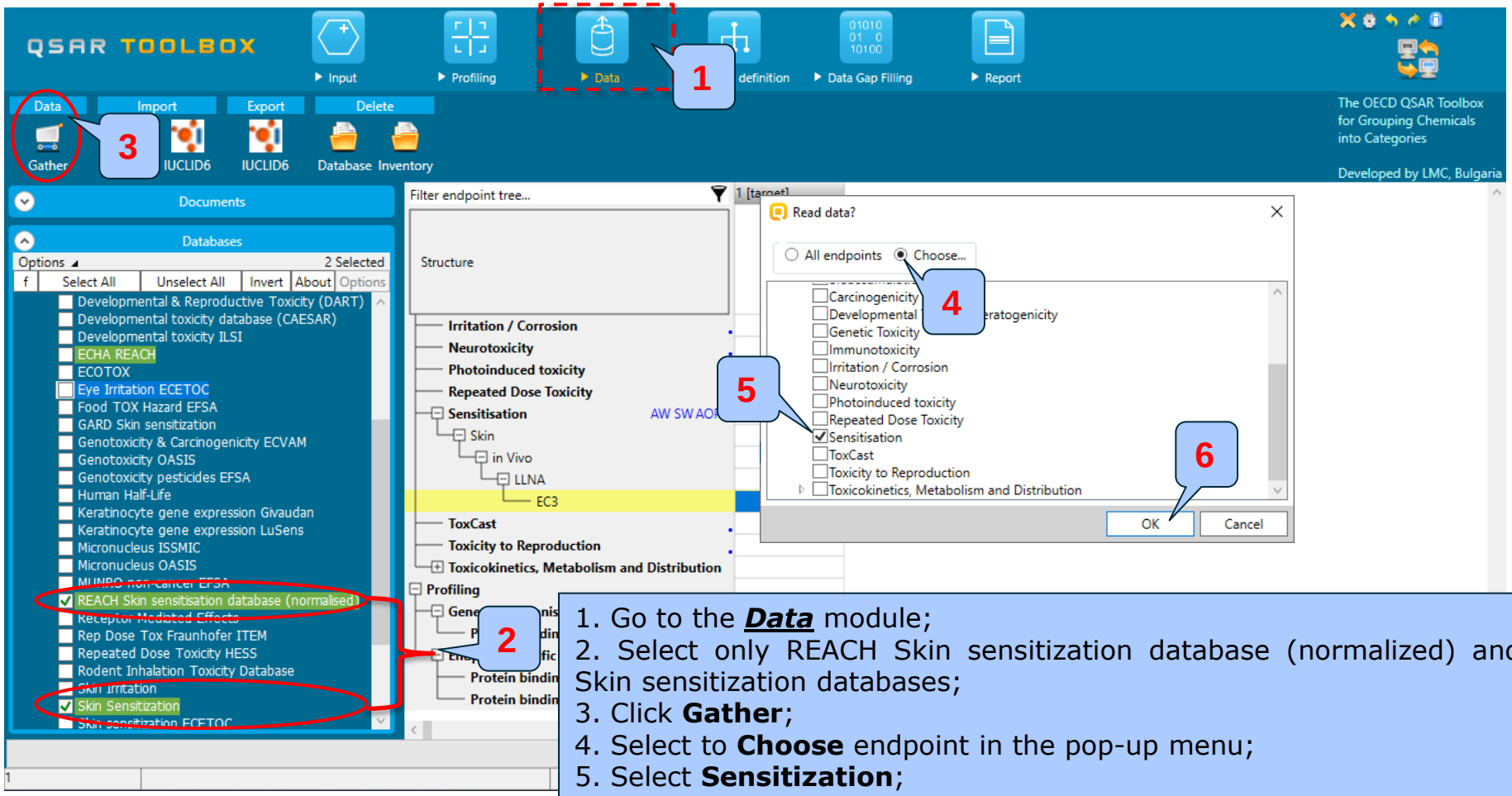
Data
Overview

- "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
Case study

- In this example, we limit our data gathering to a single toxicity endpoint (skin sensitization).
- In case of defined endpoint, the databases containing data for this endpoint, will be highlighted in green. The user could select all or just some of them.

Data
Gather data



1. Go to the ***Data*** module;
2. Select only REACH Skin sensitization database (normalized) and Skin sensitization databases;
3. Click **Gather**;
4. Select to **Choose** endpoint in the pop-up menu;
5. Select **Sensitization**;
6. Confirm by **OK**.

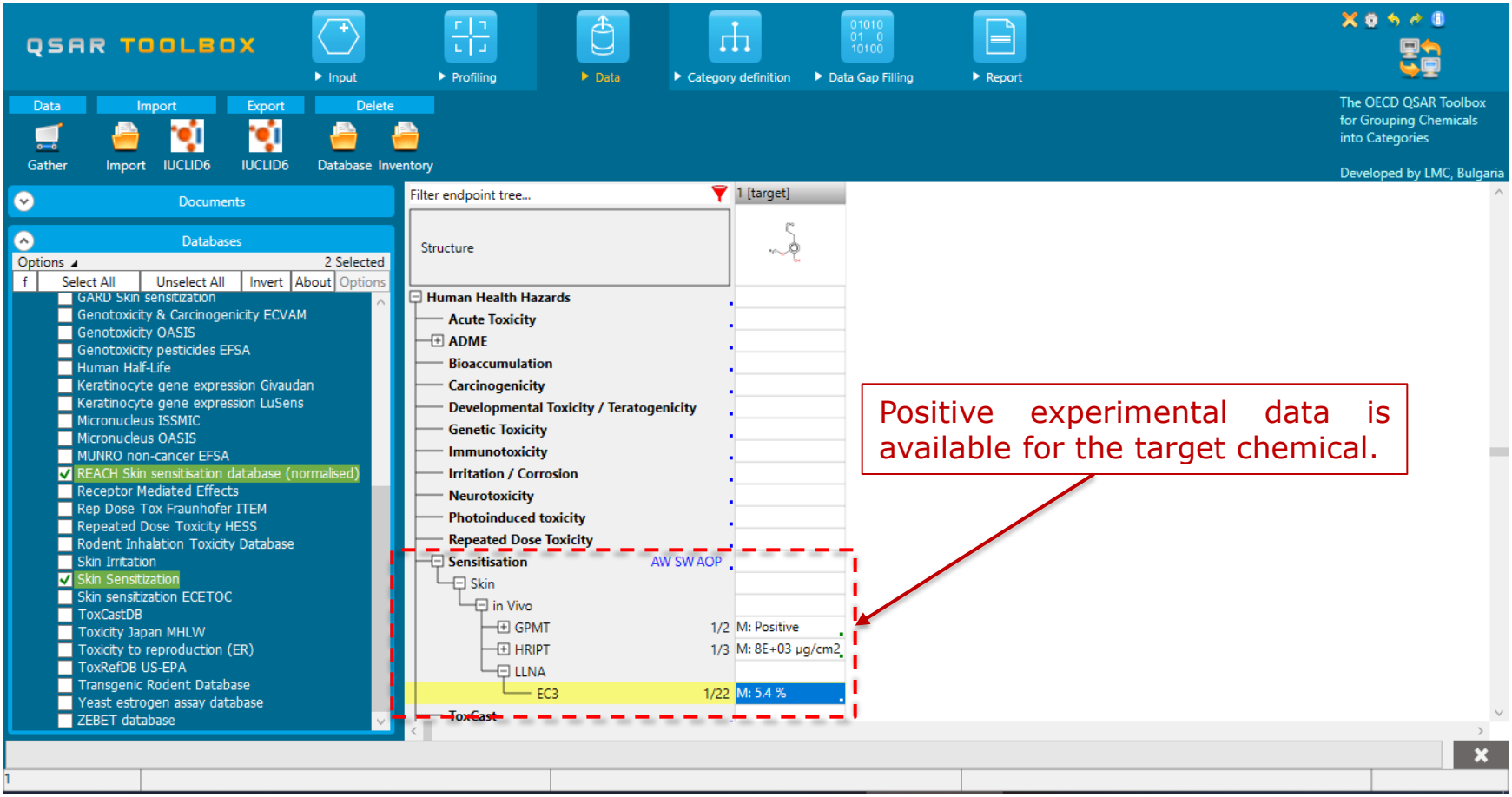
Data
Gather data

- Toxicity information on the target chemical is electronically collected from the selected dataset(s).

- It should be kept in mind that the search for data and analogues is performed only among the chemicals which are listed in the selected databases, which in this example are **Skin sensitization** and **REACH Skin sensitisation database (normalised).**

- In this example, Positive experimental data is available for the target chemical (see next screen shots)

Data
Available experimental data



Recap

- In the first module (*Input*) we:
  - entered the target chemical by CAS;
  - selected the chemical with High reliability of the CAS/SMILES correlation;
  - defined the target endpoint.
- In the second module (*Profiling*) we:
  - selected the profilers related to the target endpoint (highlighted in green);
  - saw that there is no PBA in target molecule.
- In the third module (*Data*), we:
  - selected two databases containing data for the defined target endpoint (*Skin sensitization* and *REACH Skin sensitisation database (normalised)*)
  - saw that positive skin sensitization data is available for the target chemical.

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Data
  - **Category definition**

Category Definition
Grouping methods

- The different grouping methods allow the user to group chemicals into chemical categories according to different measures of "similarity" so that within a category data gaps can be filled by read-across.

Category Definition
Suitable Categorization/Assessment Phases

Suitable categorization phases:

1. Structure-related profilers
2. Endpoint specific profilers (for sub-categorization)
3. Additional structure-related profilers, if needed to eliminate dissimilar chemicals (to increase the consistency of category) (e.g. chemical elements)

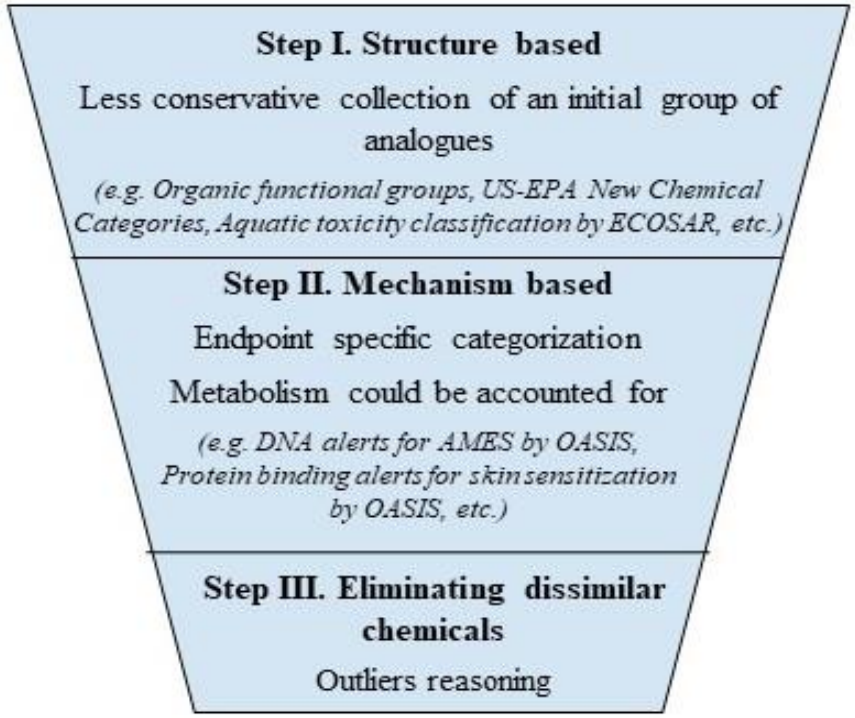
Performing categorization:

1. The categorization phases should be applied successively
2. The application order of the phases depend on the specificity of the data gap filling
3. More categories of same Phase could be used in forming categories
4. Some of the phases could be skipped if consistency of category members is reached

Graphical illustration of the suitable categorization phases is shown on next slide

Category Definition

Suitable Categorization/Assessment Phases



Broad grouping
Endpoint Non-specific

Subcategorization
Endpoint Specific

Subcategorization
Endpoint Non-specific

Note: As long as an acceptable level of structural and mechanistic similarity is achieved, it is not mandatory to follow all the stages described in the order given above; they can be executed differently or even skipped.
For example, in case the target chemical or any of its metabolites interact with biomacromolecules via a clearly defined mechanism relevant for the endpoint to predict, Stage I could be skipped and Stage II to be used for the primary categorization step.

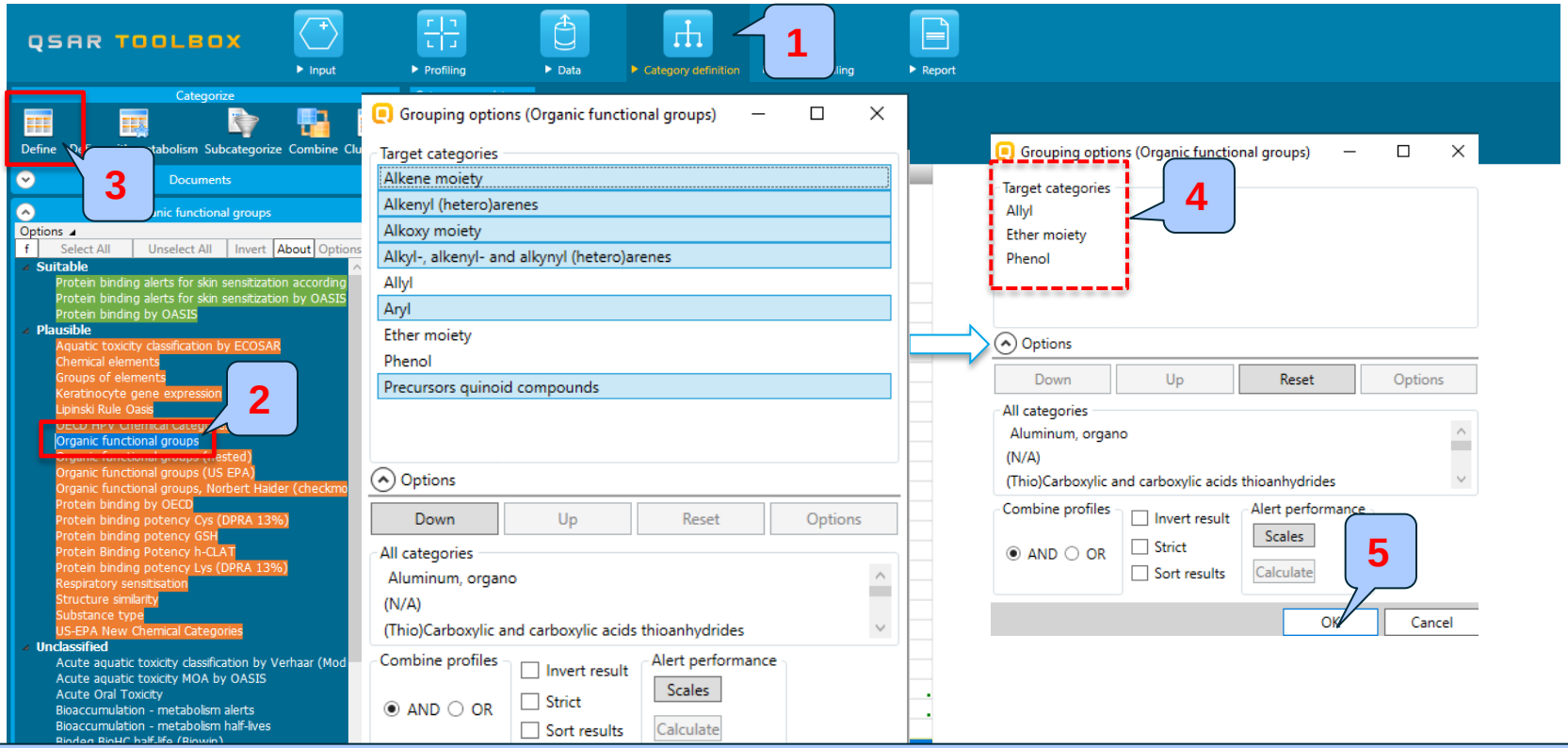
Category Definition
Suitable Categorization/Assessment Phases

- In the current example we will define a broad group of analogues using the *Organic functional groups* (OFG) profiler (step I).

- Due to the variety of OFG identifies in the target chemical, only more commonly defined functional groups (i.e. allyl, phenol, ether) will be used for searching analogues.

Category Definition

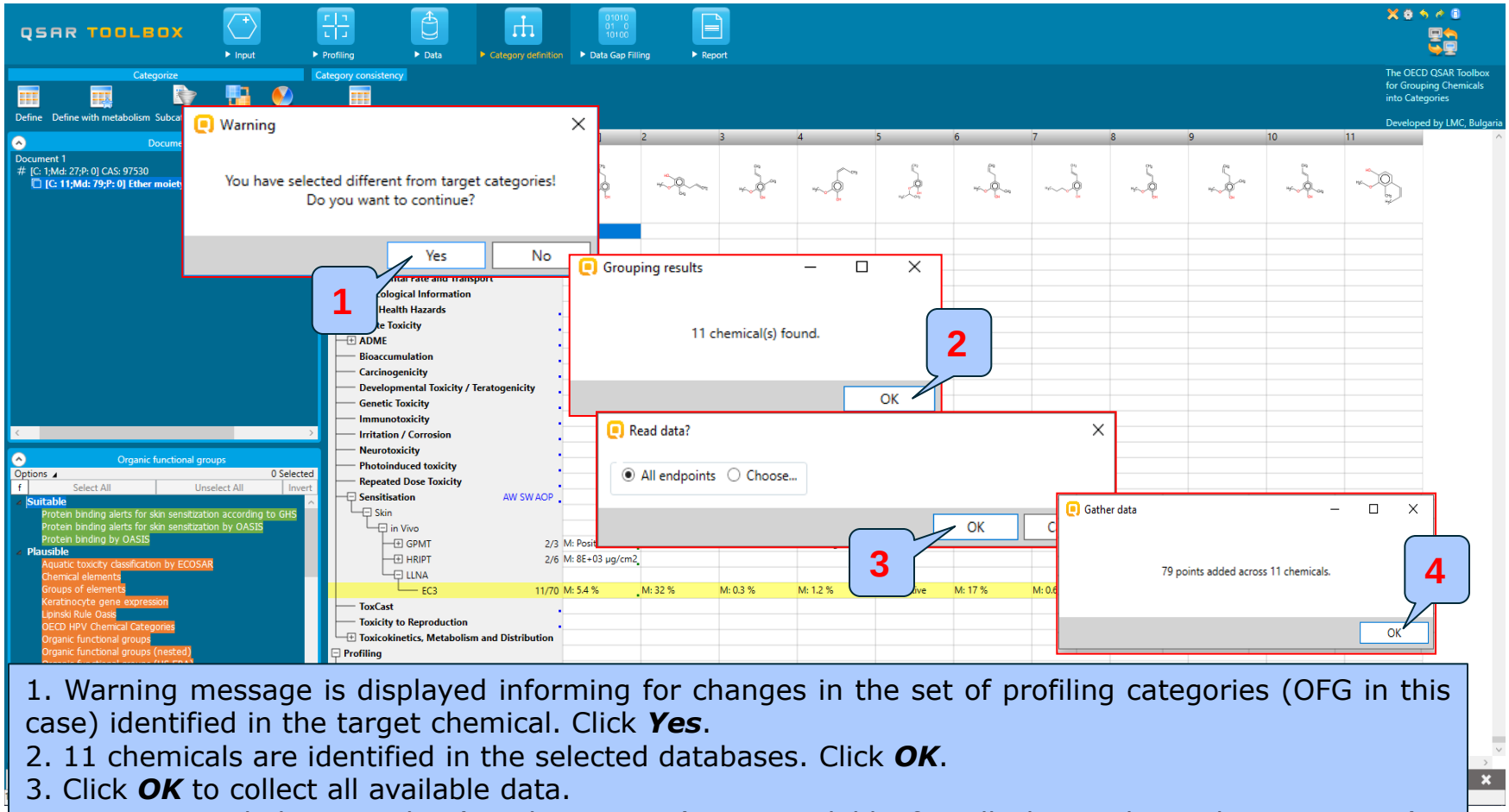
Define category by OFG



1. Go to ***Category definition*** module
2. Select ***Organic functional groups (OFG)***;
3. Click ***Define***
4. Remove all functional groups (highlighted in blue) except *Allyl*, *Ether moiety* and *Phenol* by double click one by one or press CTRL button of the keyboard, mark the undesired groups and click the **Down** button;
5. Finally click ***OK***.

Category Definition

Define category by OFG



1. Warning message is displayed informing for changes in the set of profiling categories (OFG in this case) identified in the target chemical. Click ***Yes***.
2. 11 chemicals are identified in the selected databases. Click ***OK***.
3. Click ***OK*** to collect all available data.
4. Experimental data results (79 data points) are available for all chemicals in the category (11 chemicals). Click **OK**.

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- Background
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- **Workflow**
  - Input
  - Profiling
  - Data
  - Category definition
  - **Data gap filling**

Data Gap Filling
Overview

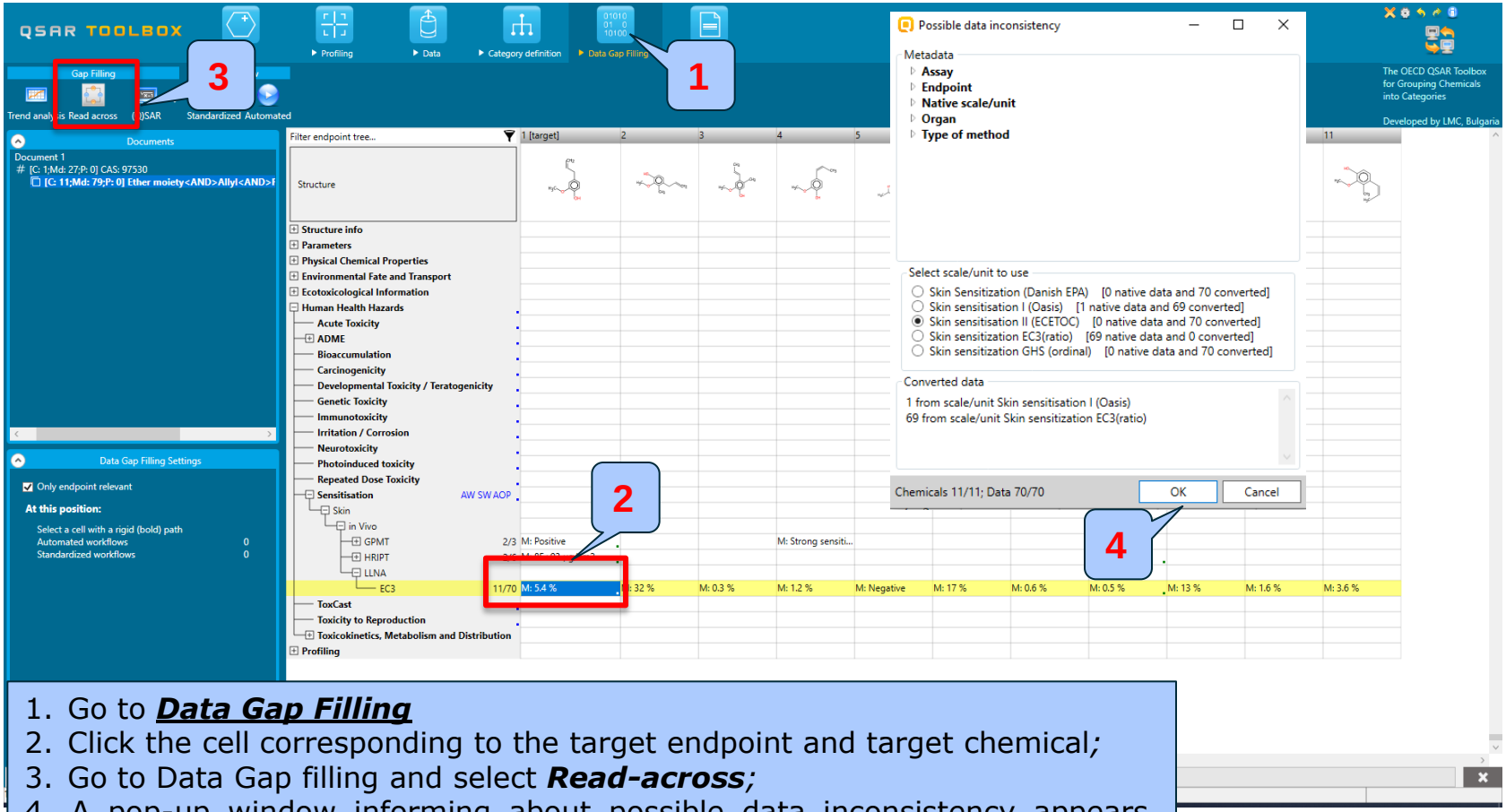
- "Data Gap Filling" module provides three different data gap filling tools:
  - Read-across
  - Trend analysis
  - (Q)SAR models

- The most relevant data gap mechanism should be used by taking into account the following considerations:
  - Read-across is the appropriate data-gap filling method for "qualitative" endpoints like skin sensitisation or mutagenicity for which a limited number of results are possible (e.g. positive, negative, equivocal). Furthermore read-across is recommended for "quantitative endpoints" (e.g., 96h-LC50 for fish) if only a low number of analogues with experimental results are identified.
  - Trend analysis is the appropriate data-gap filling method for "quantitative endpoints" (e.g., 96h-LC50 for fish) if a high number of analogues with experimental results are identified.
  - "(Q)SAR models" can be used to fill a data gap if no adequate analogues are found for a target chemical.

- In this example, we will use read-across.

Data Gap Filling

Apply Read-across



1. Go to ***Data Gap Filling***
2. Click the cell corresponding to the target endpoint and target chemical;
3. Go to Data Gap filling and select ***Read-across***;
4. A pop-up window informing about possible data inconsistency appears. Confirm the default scale with **OK**.

More details about scale definitions is provided on next slide.

Data Gap Filling
Sidebar on the data scales

- The available data in the databases could be represented in different scales depending on the database` donators.
- The skin sensitisation data could be: 1) categorical (for example: positive; negative; weak sensitizer; strong sensitizer, etc.) or 2) numerical (e.g. EC3 values in percentage).
- The main purpose of the scales is to unify all data available in the Toolbox databases for a certain endpoint by making conversions between them.
- The default scale for Skin Sensitisation is "*Skin Sensitisation ECETOC*". It converts all skin data into dichotomous scale: Positive/Negative.

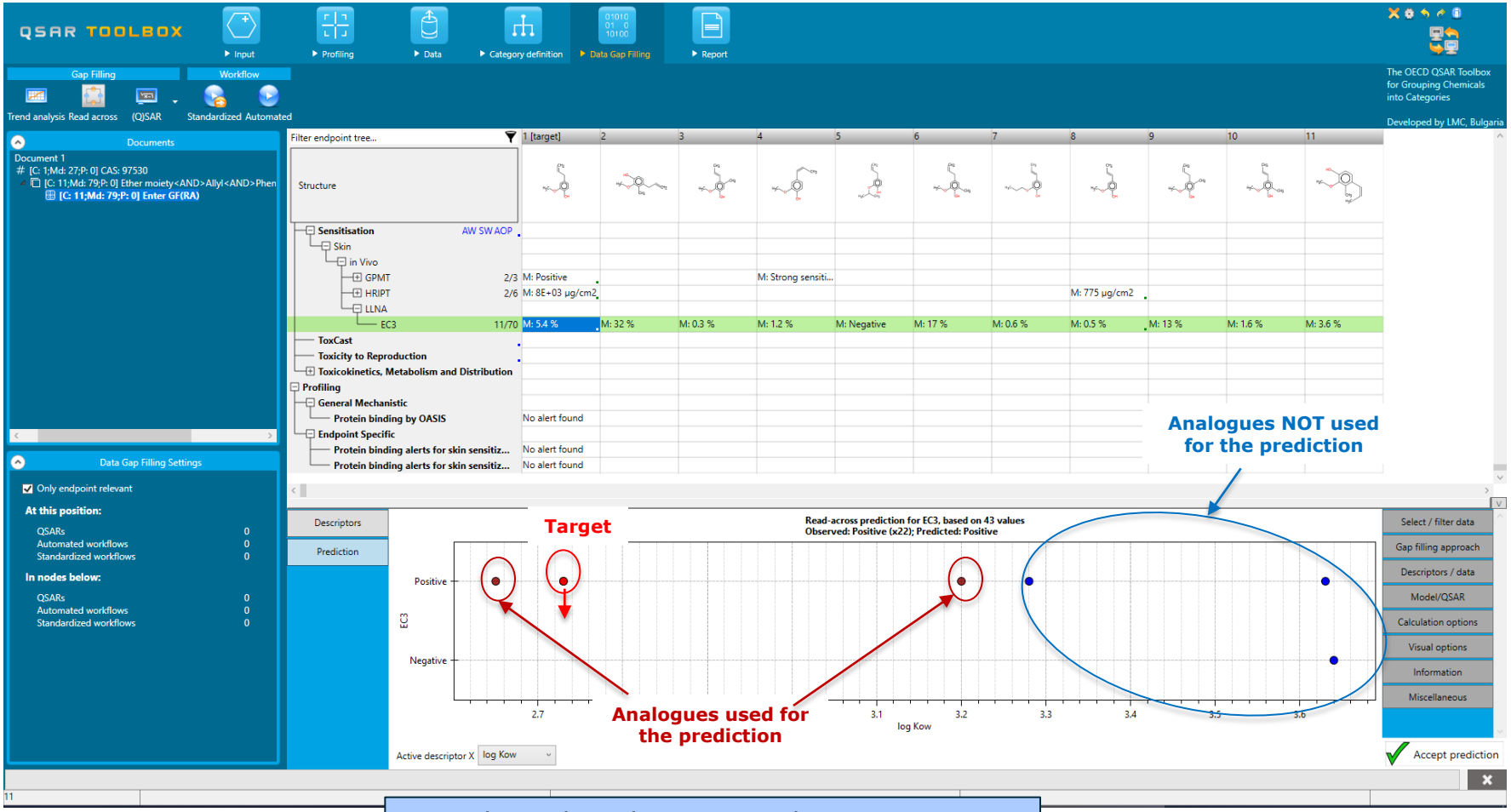
Data Gap Filling
Data Gap Filling graph

- The resulting graph is experimental results of all analogues (Y axis) according to a descriptor (X axis) with the default descriptor of log Kow (see next screen shot).
- The **RED** dot represents predicted result for the target chemical;
- The **BROWN** dots represent the experimental results available for the analogues that are used for the read-across. By default the closest five analogues are used for the prediction;
- The **BLUE** dot represents the experimental results available for the analogues that are not used for read-across.

Note: In some case one brown/blue point could correspond to more than one chemical. This holds for structures (e.g. different isomers) having the same X axis descriptor value (e.g. logKow) and the same Y axis descriptor value (e.g. positive).

Data Gap Filling

Read-across



Initial graph without any subcategorization.

Data Gap Filling
Subcategorizations

- The category could be further narrowed-down by using of some of the endpoint-specific or structure-based profilers. This aim to reduce the uncertainty among the category members.

- The following profilers will be used for subcategorization:

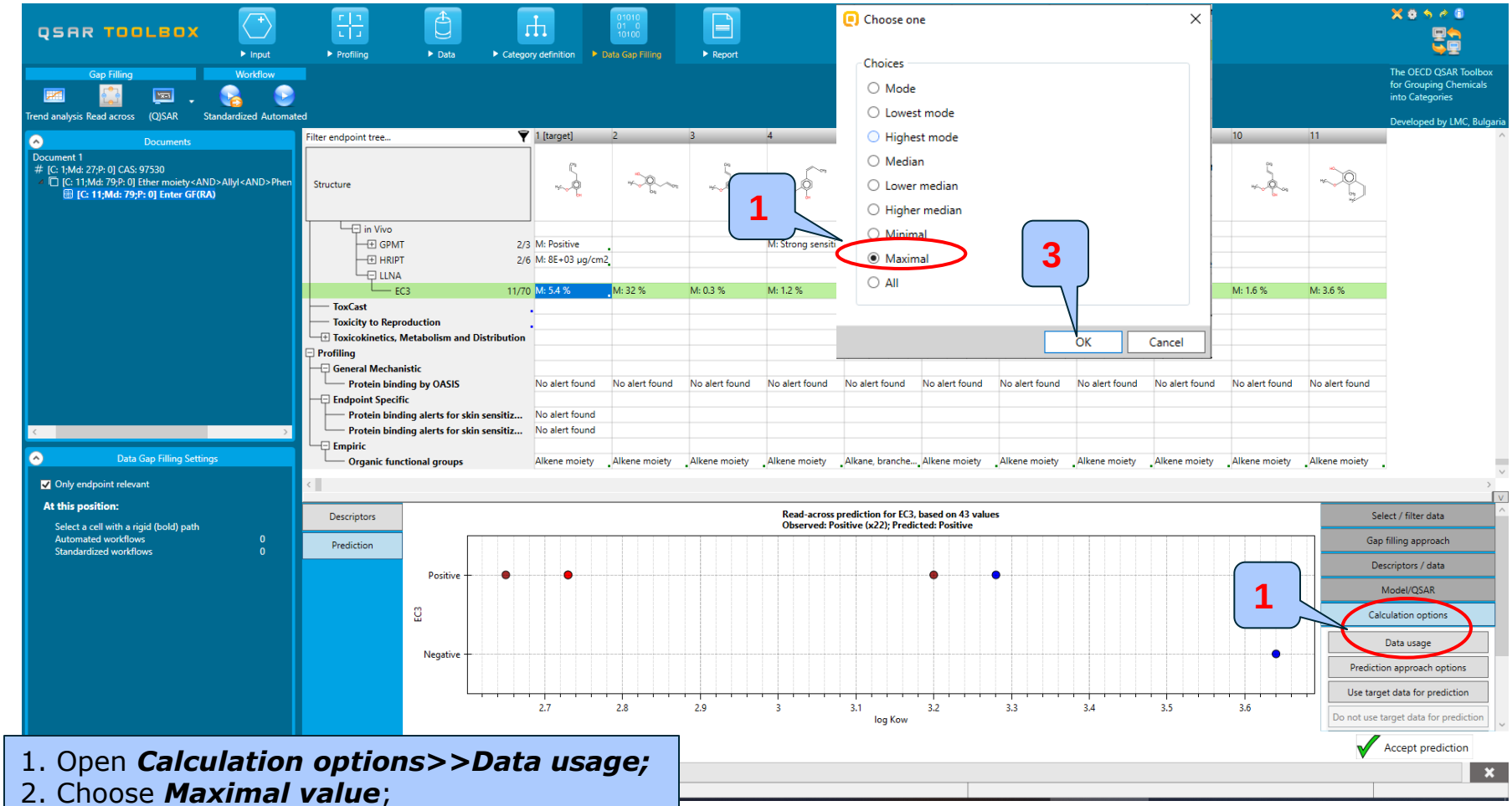
  1) O*rganic functional group* – step I of the categorization process (see slide 36) is repeated in order to eliminate multifunctional analogues

  2) Protein binding alerts for skin sensitization by OASIS

  3) Protein binding alerts for skin sensitization by OASIS combined with *Autoxidation simulator*

- These steps are summarized in the next screen shots. Before subcategorizations maximal values are taken into account

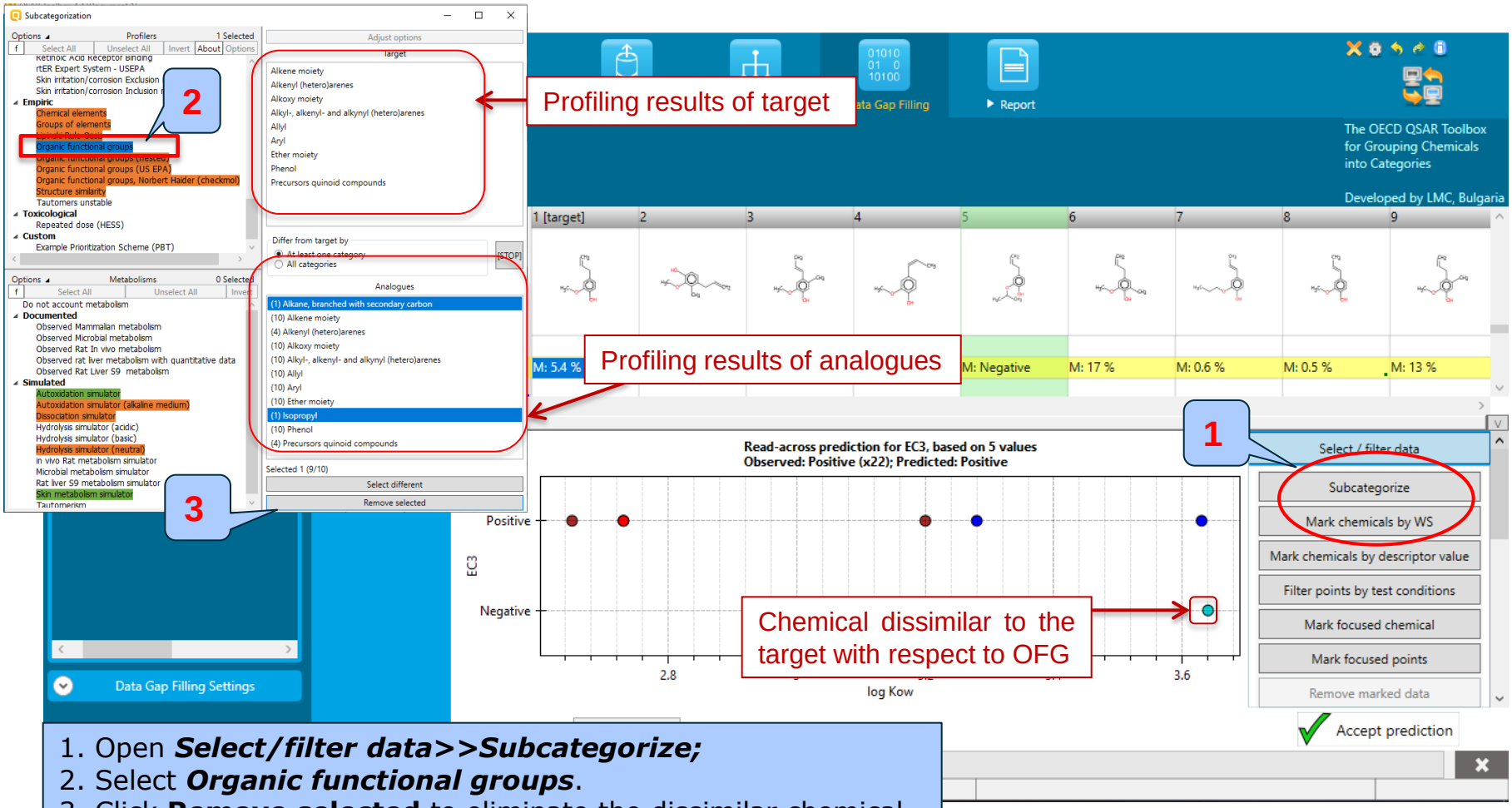
Data Gap Filling
Subcategorizations



1. Open ***Calculation options>>Data usage;***
2. Choose ***Maximal value***;
3. Click **OK**.

Data Gap Filling

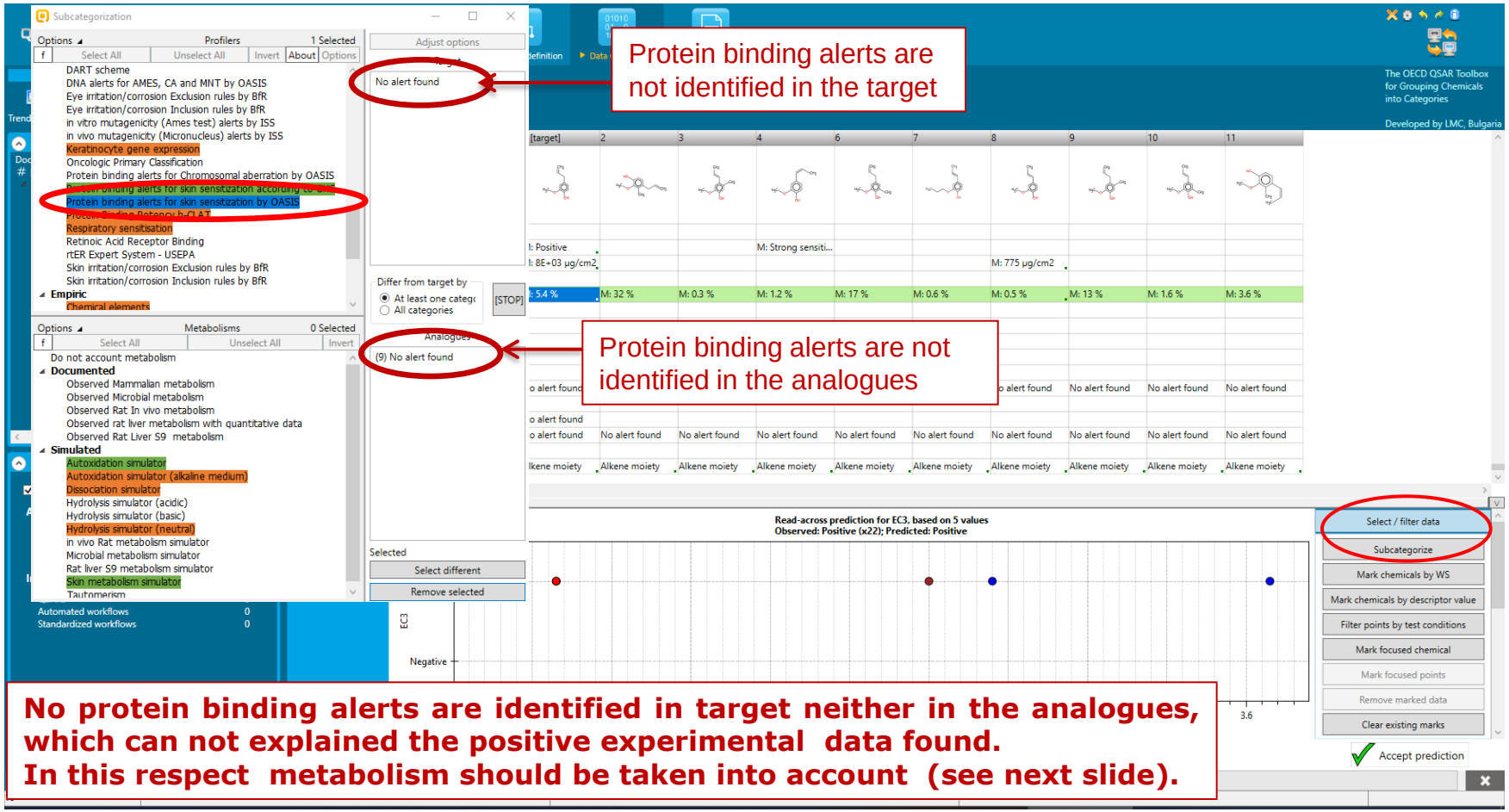
Subcategorization 1: Organic functional groups



1. Open ***Select/filter data>>Subcategorize;***
2. Select ***Organic functional groups***.
3. Click **Remove selected** to eliminate the dissimilar chemical.

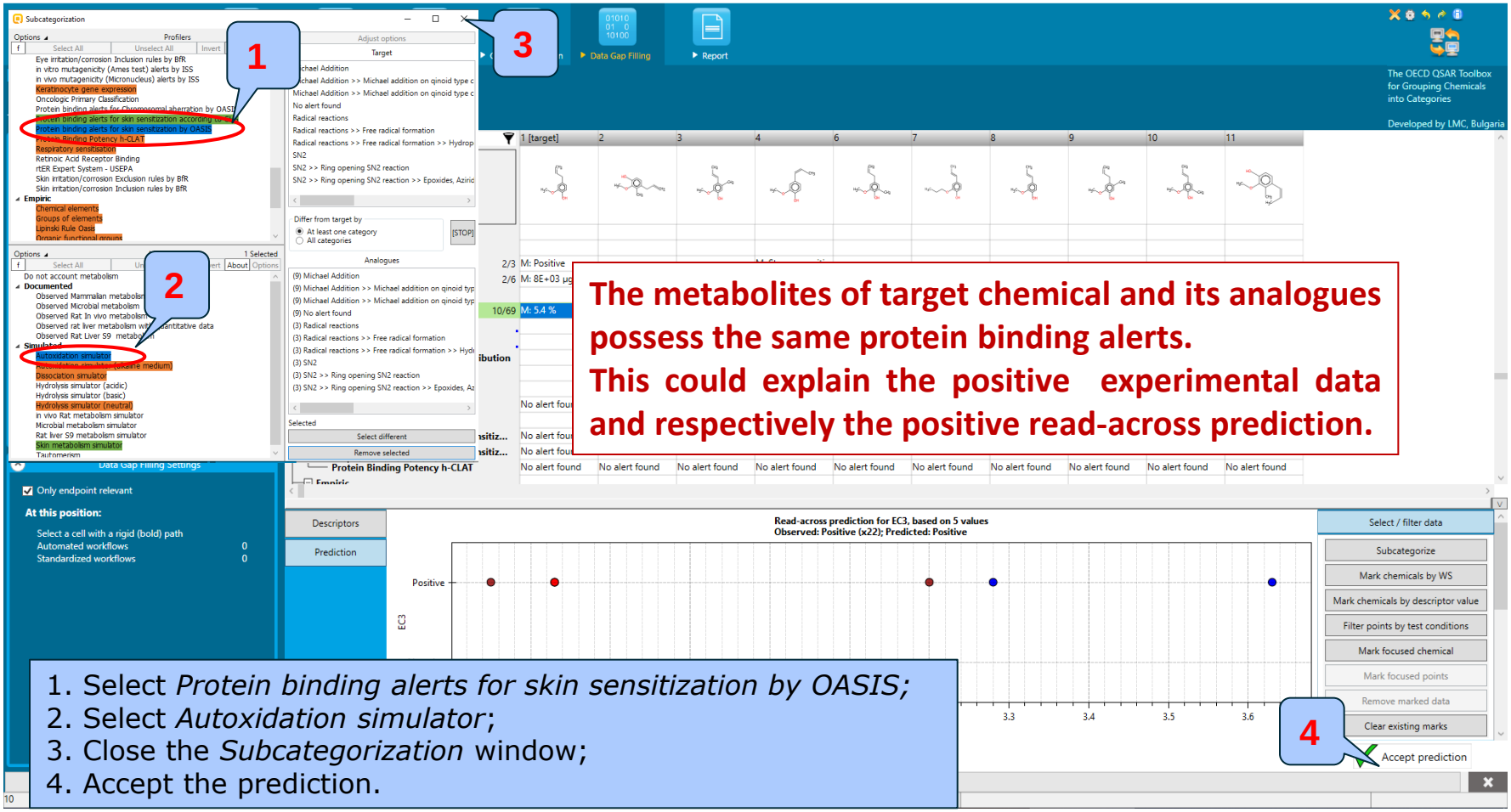
Data Gap Filling

Subcategorization 2: Protein binding alerts for skin sensitization by OASIS



Data Gap Filling

Subcategorization 3: Protein binding alerts for skin sensitization by OASIS combined with Autoxidation simulator



1. Select *Protein binding alerts for skin sensitization by OASIS;*
2. Select *Autoxidation simulator*;
3. Close the *Subcategorization* window;
4. Accept the prediction.

Data Gap Filling
Interpreting Read-across

- In this example the target and all analogues have no protein binding alerts as parents.
- The target and all analogues have the same protein binding alerts when autoxidation is taken into account.
- The latter could explain the positive experimental data of the target and the analogues.

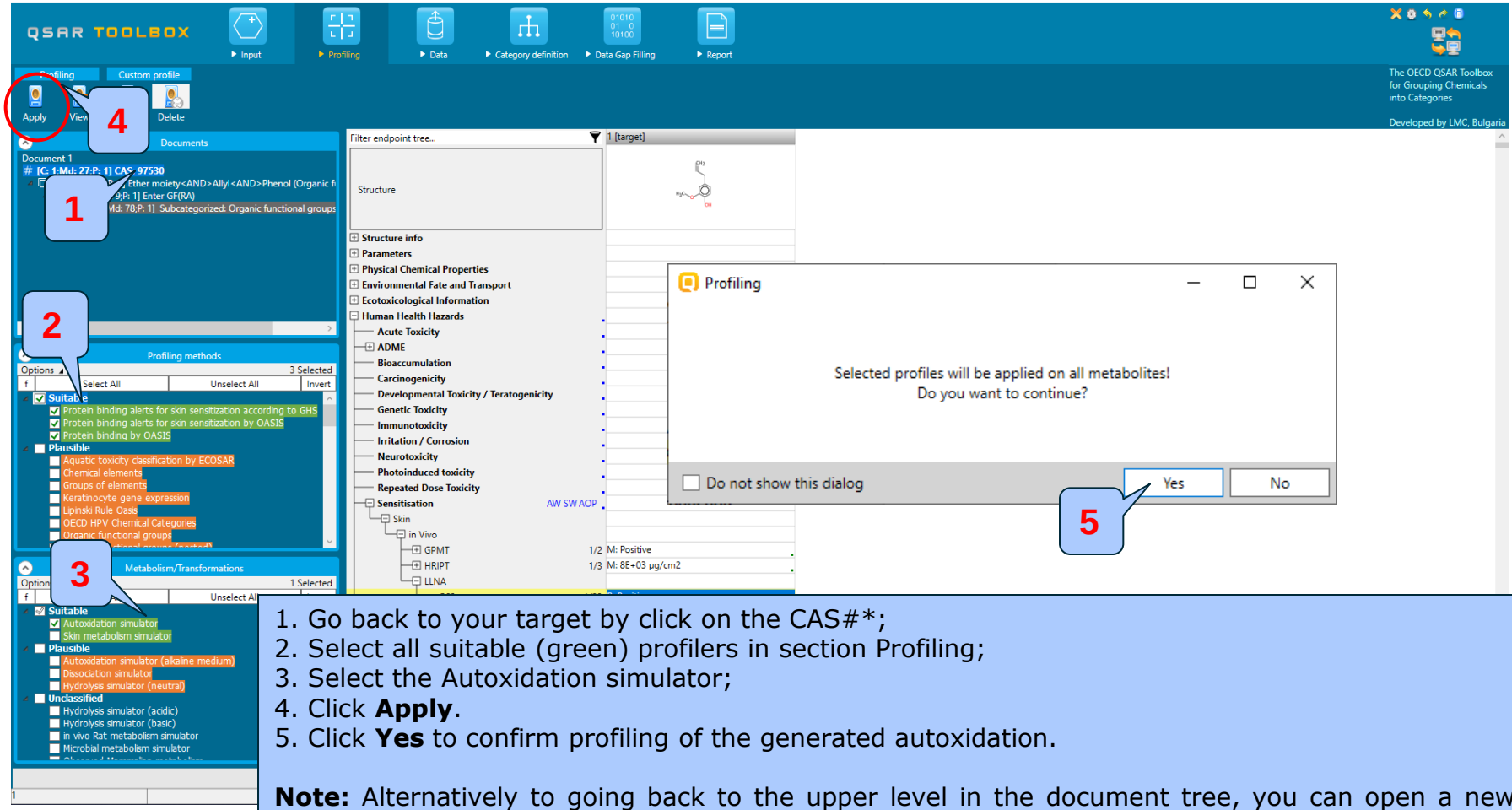
Data Gap Filling
Next actions

- The study continues with a second scenario for predicting the skin sensitization potential of eugenol where a category with analogues will be defined accounting for the abiotic activation of the target.

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - **Profiling of (a)biotic products**

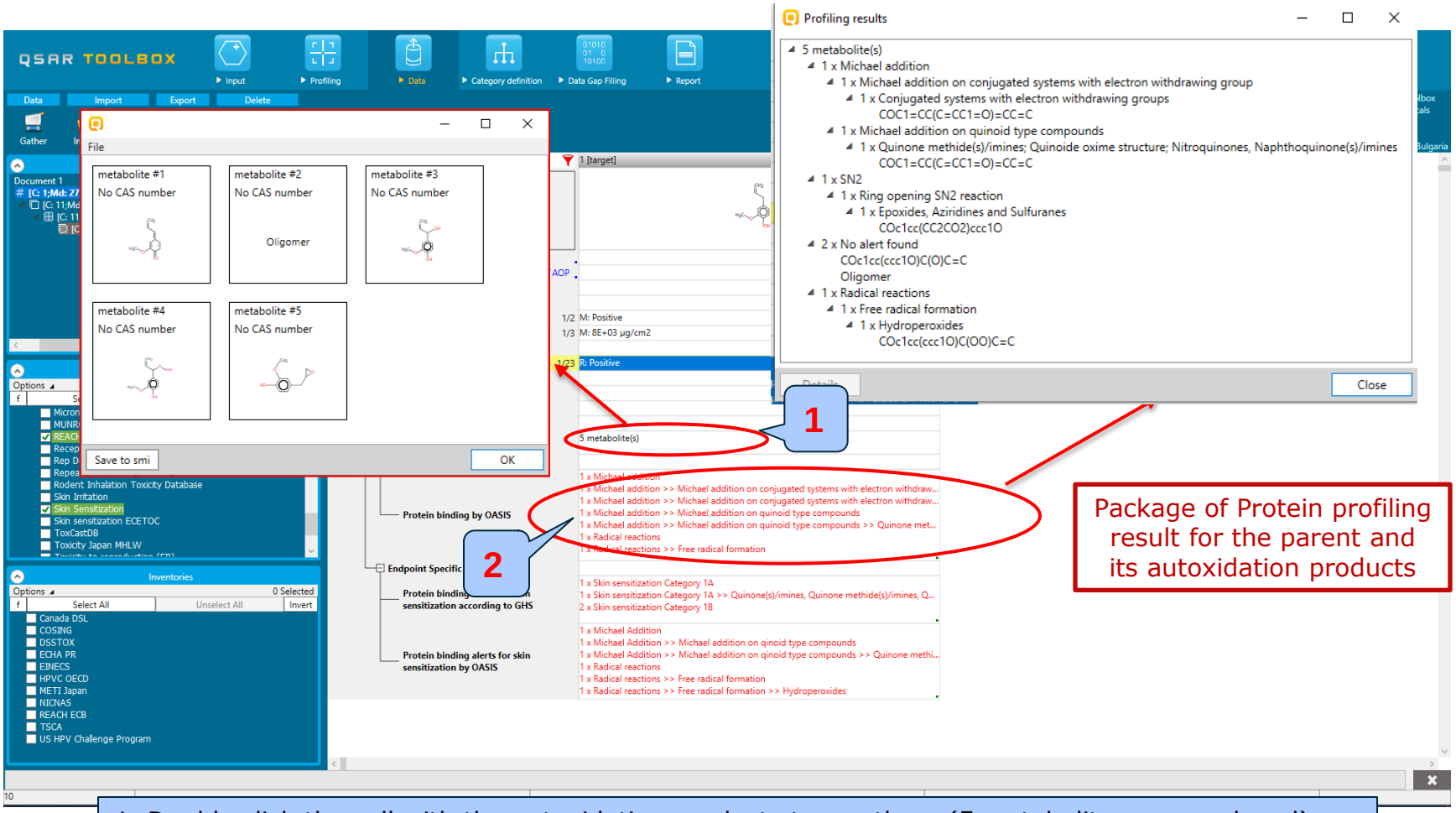
Profiling of (a)biotic products



1. Go back to your target by click on the CAS#*;
2. Select all suitable (green) profilers in section Profiling;
3. Select the Autoxidation simulator;
4. Click **Apply**.
5. Click **Yes** to confirm profiling of the generated autoxidation.

Note: Alternatively to going back to the upper level in the document tree, you can open a new document, repeat the steps described in slides 15 and 17 and then to continue with the current example.

Profiling of (a)biotic products

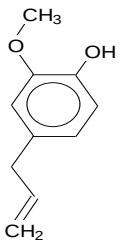


1. Double click the cell with the autoxidation products to see them (5 metabolites are produced);
2. Double click the cell with profiling results identified in the metabolites.

Recap

Parent

Eugenol
CAS# 97-93-0



Protein binding alert in the parent
(Protein binding by OASIS)

No alert found

Experimental data

LLNA Strong sensitizer

Categorization

Organic functional groups

Data gap filling

No protein binding alerts
Positive RA prediction

How to explain positive RA ?

Metabolites

5 autoxidation products

Protein binding alert in the metabolites
(Protein binding by OASIS + Autoxidation simulator)

Protein binding alerts identified in the package of metabolites

next

Categorization with metabolism

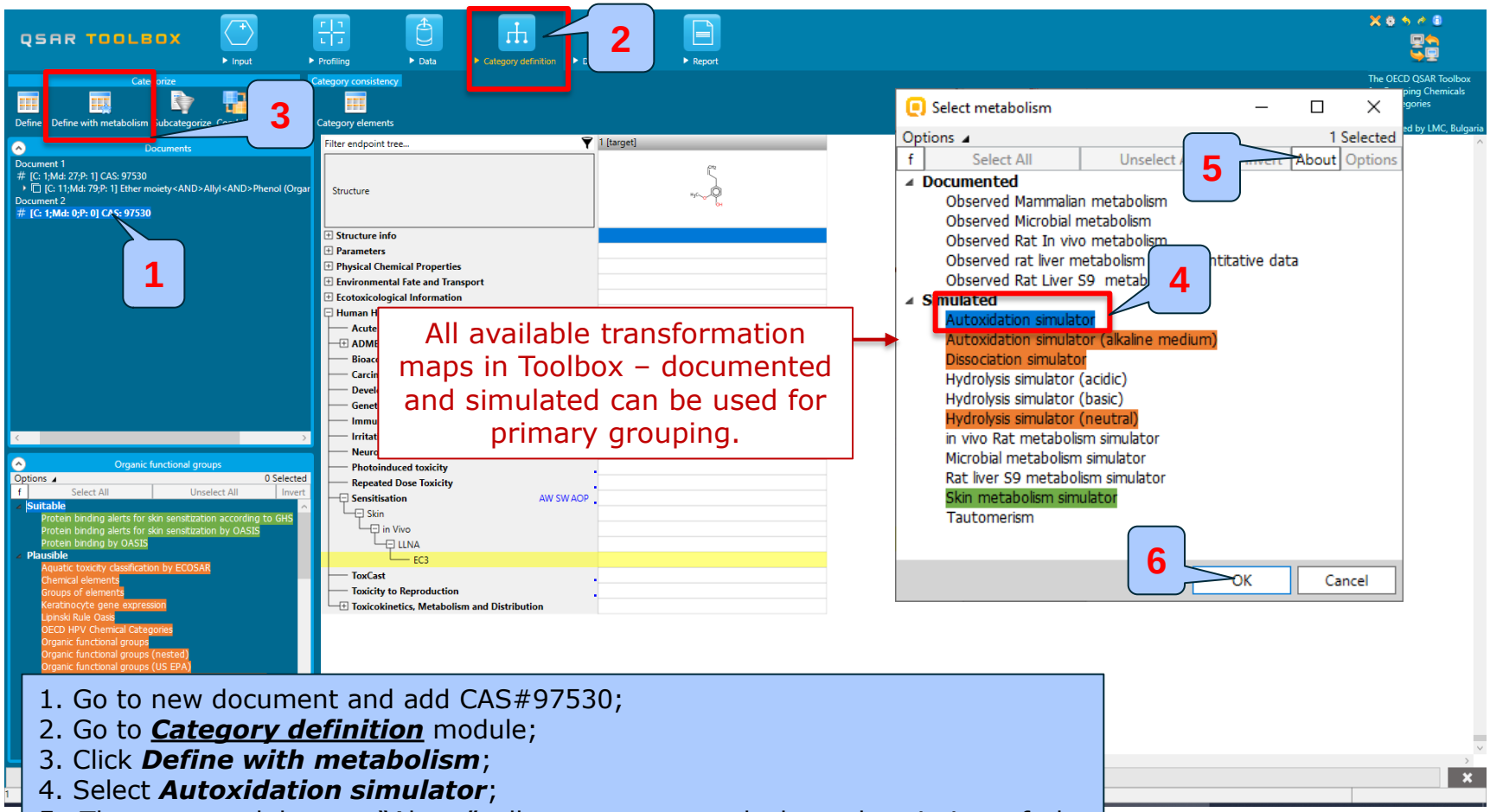
Identifying analogues of the target taking into account its metabolic activation

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling of (a)biotic products
  - **Category definition based on (a)biotic transformations**

Category definition based on (a)biotic transformations

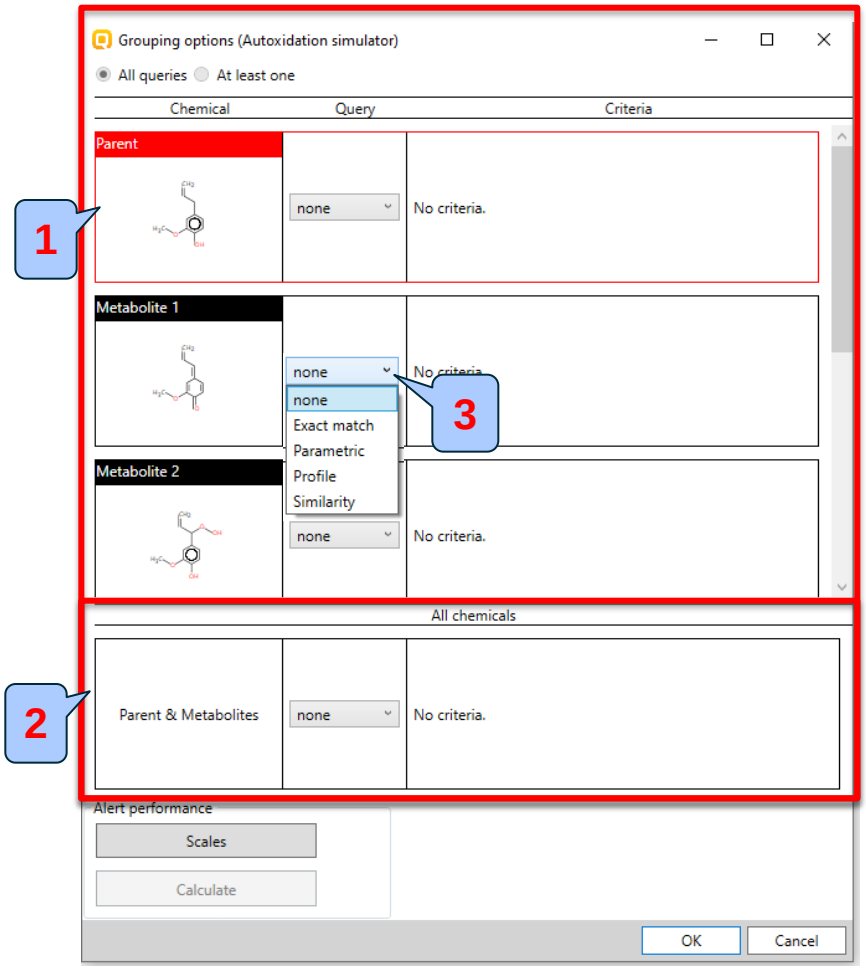
Define category using autoxidation simulator



1. Go to new document and add CAS#97530;
2. Go to ***Category definition*** module;
3. Click ***Define with metabolism***;
4. Select ***Autoxidation simulator***;
5. The appeared button "About" allows you to read short description of the simulator;
6. Click ***OK.***

Category definition based on (a)biotic transformations

Grouping options window



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 one, i.e. the criteria is provided for the whole package "parent and metabolites" but not for the individual metabolites.

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

Category definition based on (a)biotic transformations
Grouping options

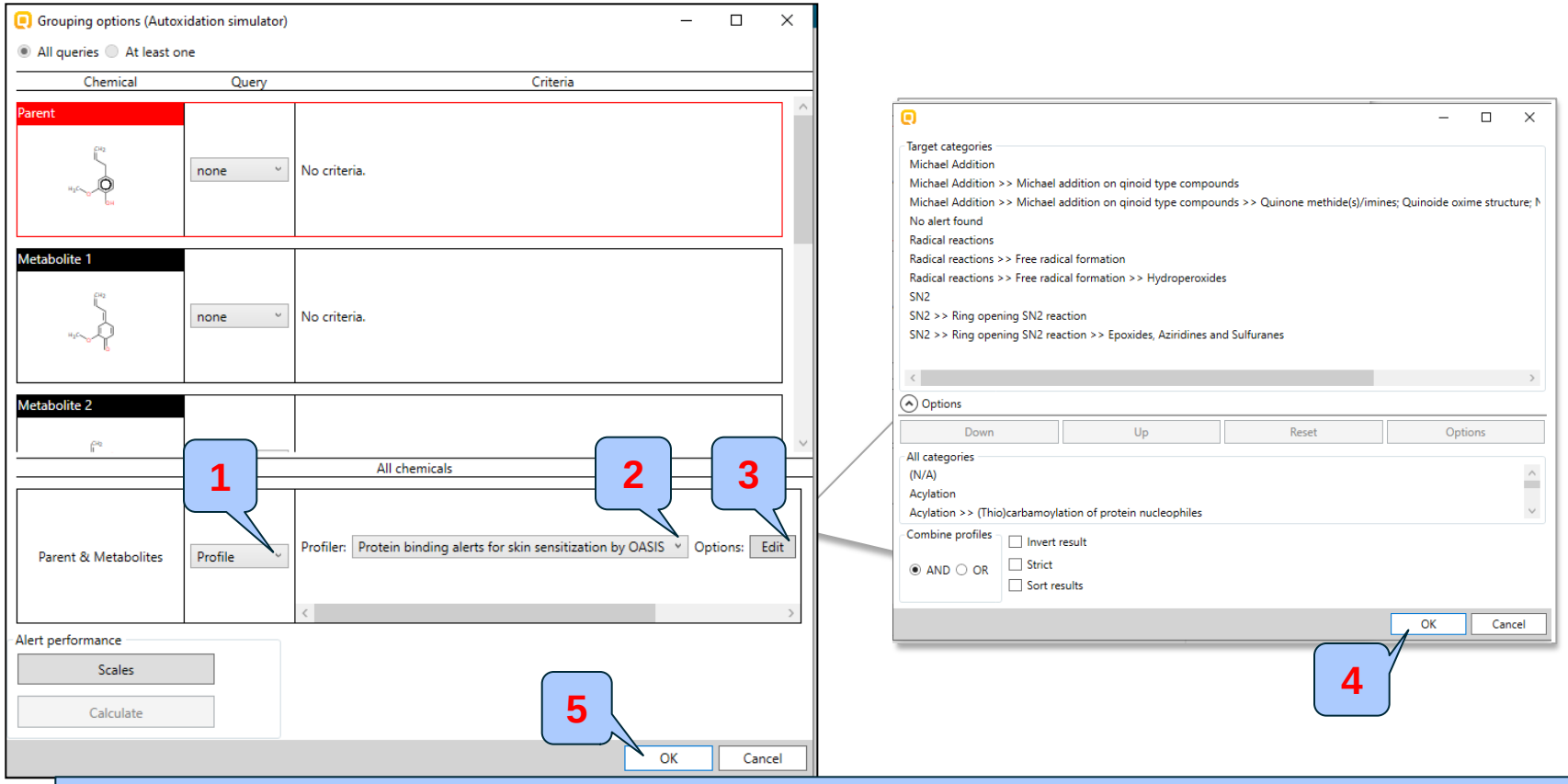
Explanation of each option from the drop down menu is given below:

- **None** – default options; no criteria is set;
- **Exact** – search for analogues which metabolites have the exact structure of the target metabolite; 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** –allows structural similarity assessment based on the atom centered fragments.

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

Category definition based on (a)biotic transformations

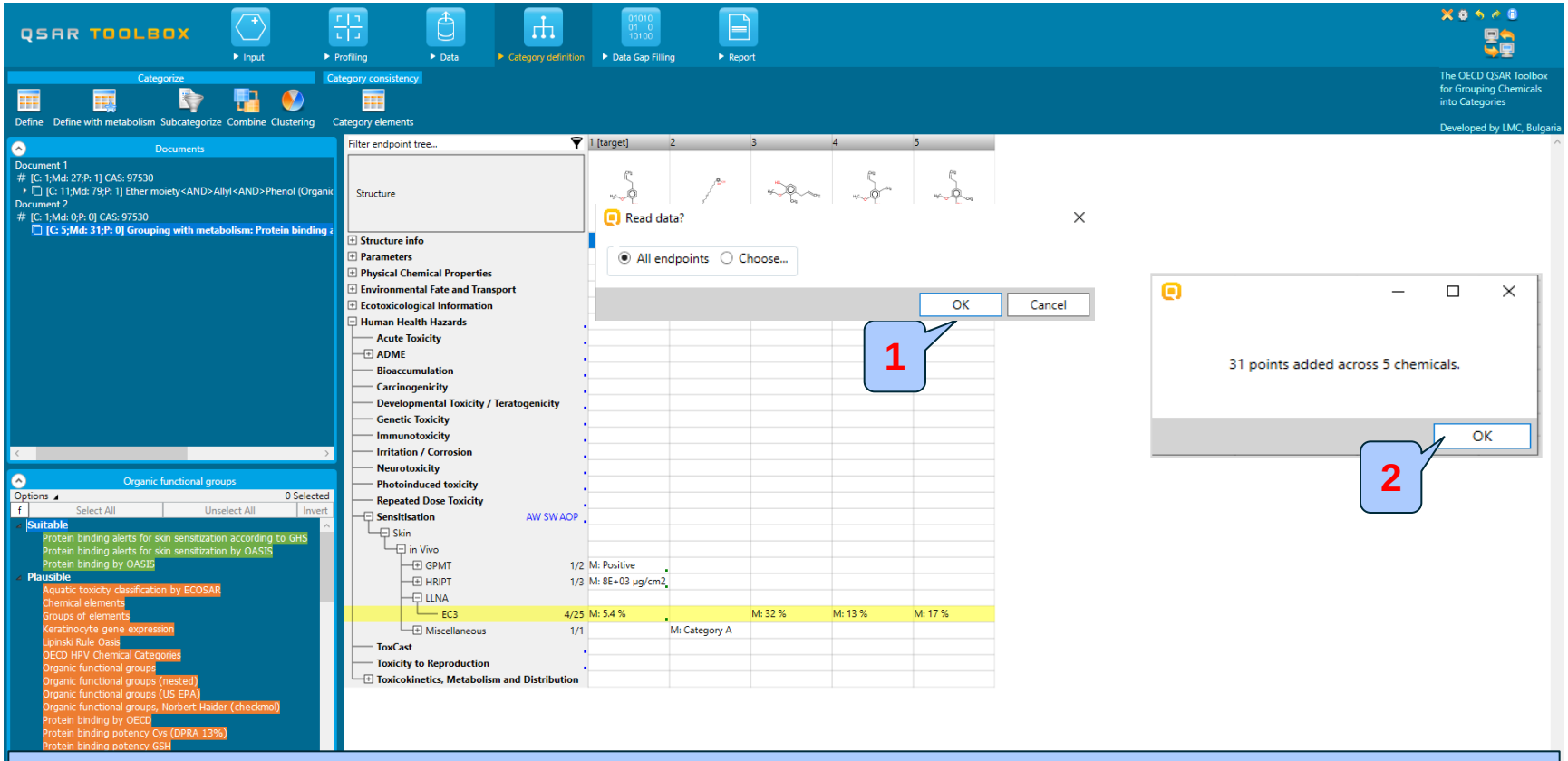
Grouping options



1. Select the **Profile** option for the package "parent & metabolites";
2. Select "*Protein binding alerts for SS by OASIS*" profile;
3. Click ***Edit*** . The profiling results of the parent structure and its metabolites are shown;
4. Click **OK** to confirm the defined search criteria;
5. Click ***OK*** in *Grouping* options window to execute the search.

Category definition based on (a)biotic transformations

Collecting data for the identified analogues

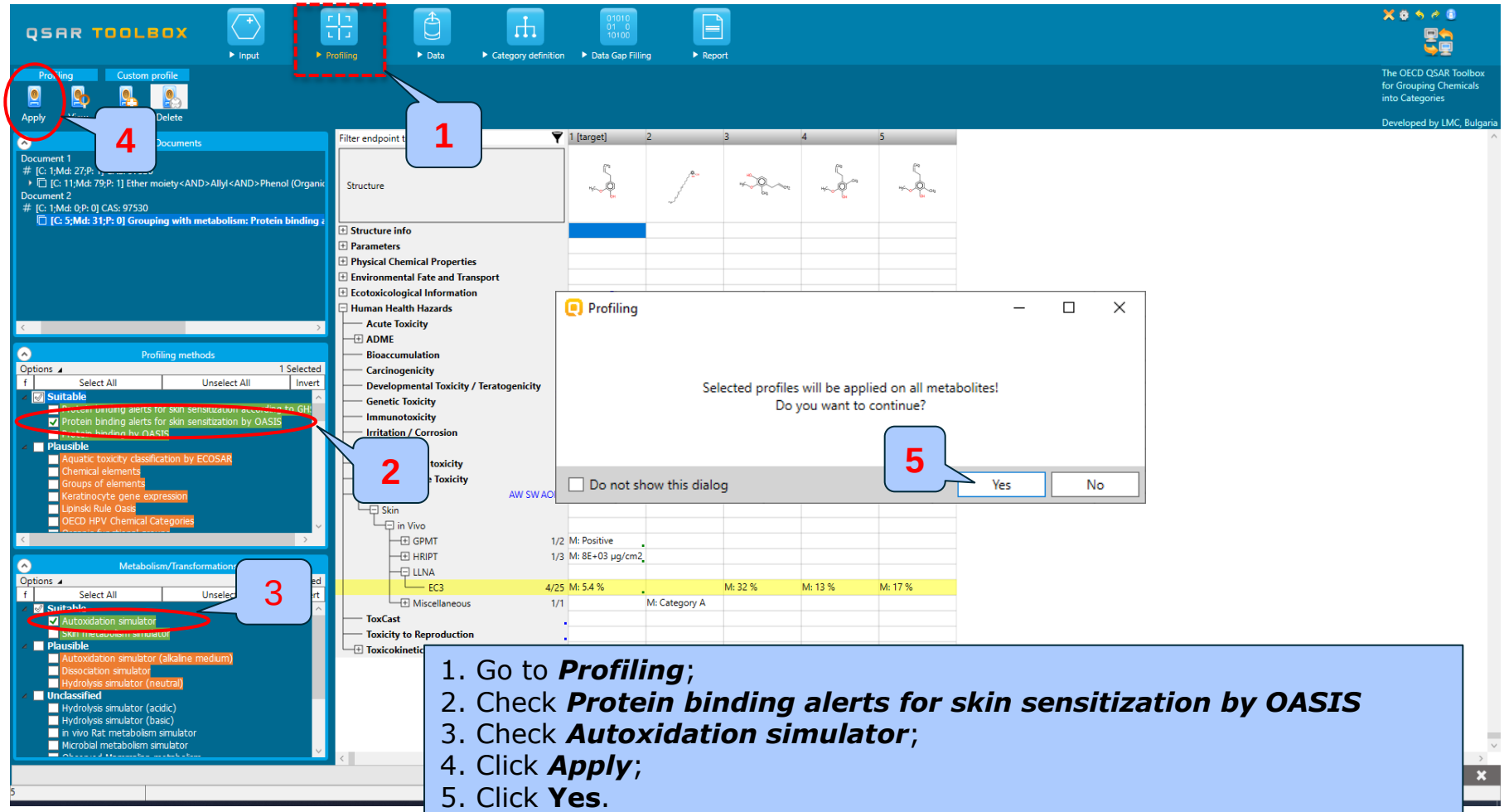


The identified chemicals appear on the data matrix.

1. Click ***OK*** to collect all data available for them;
2. 31 experimental data results are available for the five category members (1 target and 4 analogues). Click ***OK***.

Category definition based on (a)biotic transformations

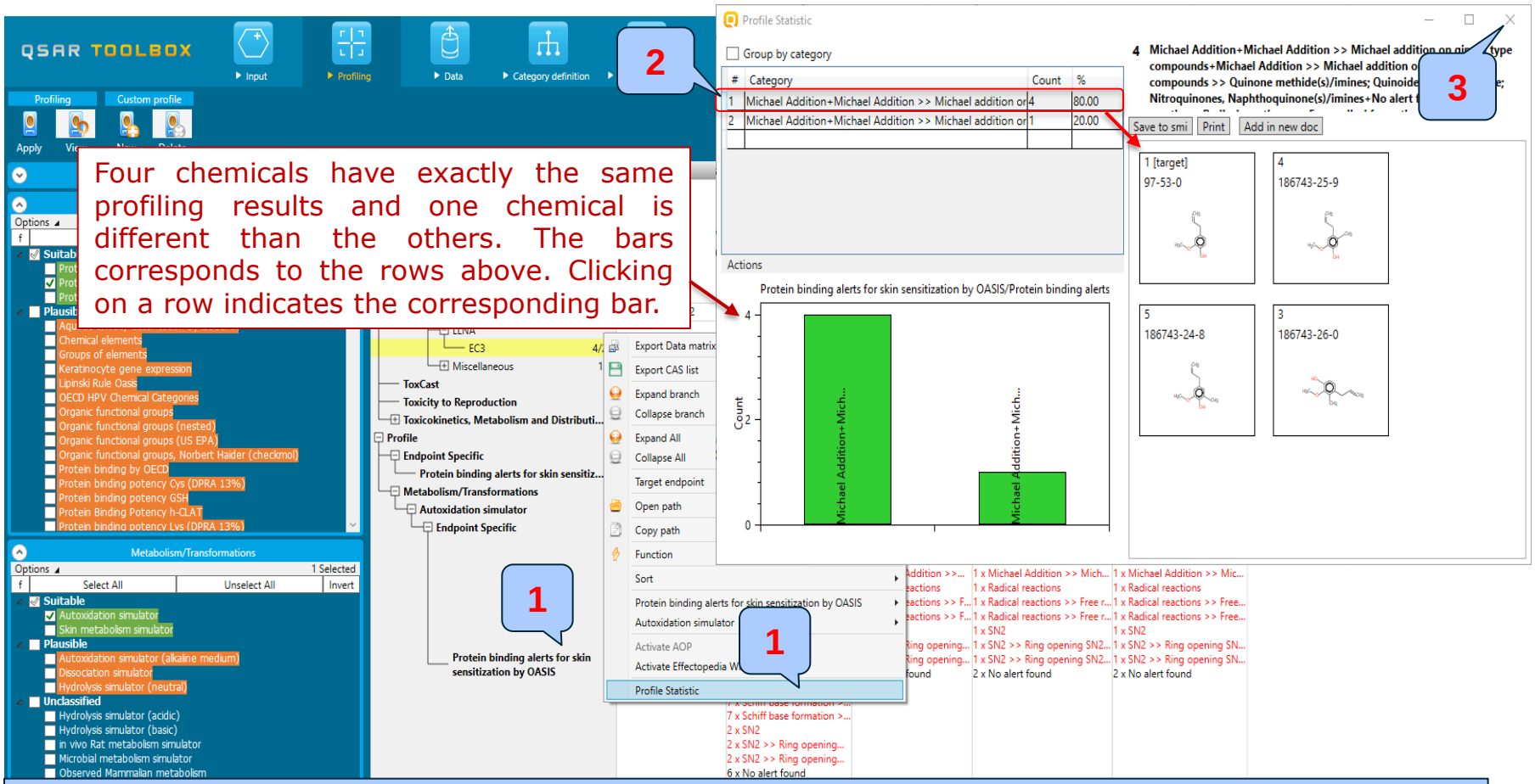
Profiling the identified analogues



1. Go to ***Profiling***;
2. Check ***Protein binding alerts for skin sensitization by OASIS***
3. Check ***Autoxidation simulator***;
4. Click ***Apply***;
5. Click **Yes**.

Category definition based on (a)biotic transformations

Profile statistic



1. Right-click next to the *Protein binding alerts for skin sensitization by OASIS* under the Metabolism/Transformations level (in the grey field). Select ***Profile statistic***.
2. Click on the first row to see the four chemicals having the exactly the same profiling results;
3. Close the *Profile statistic* window.

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling of (a)biotic products
  - Category definition based on (a)biotic transformations
  - **Data Gap Filling**

Data gap filling
Apply Read across

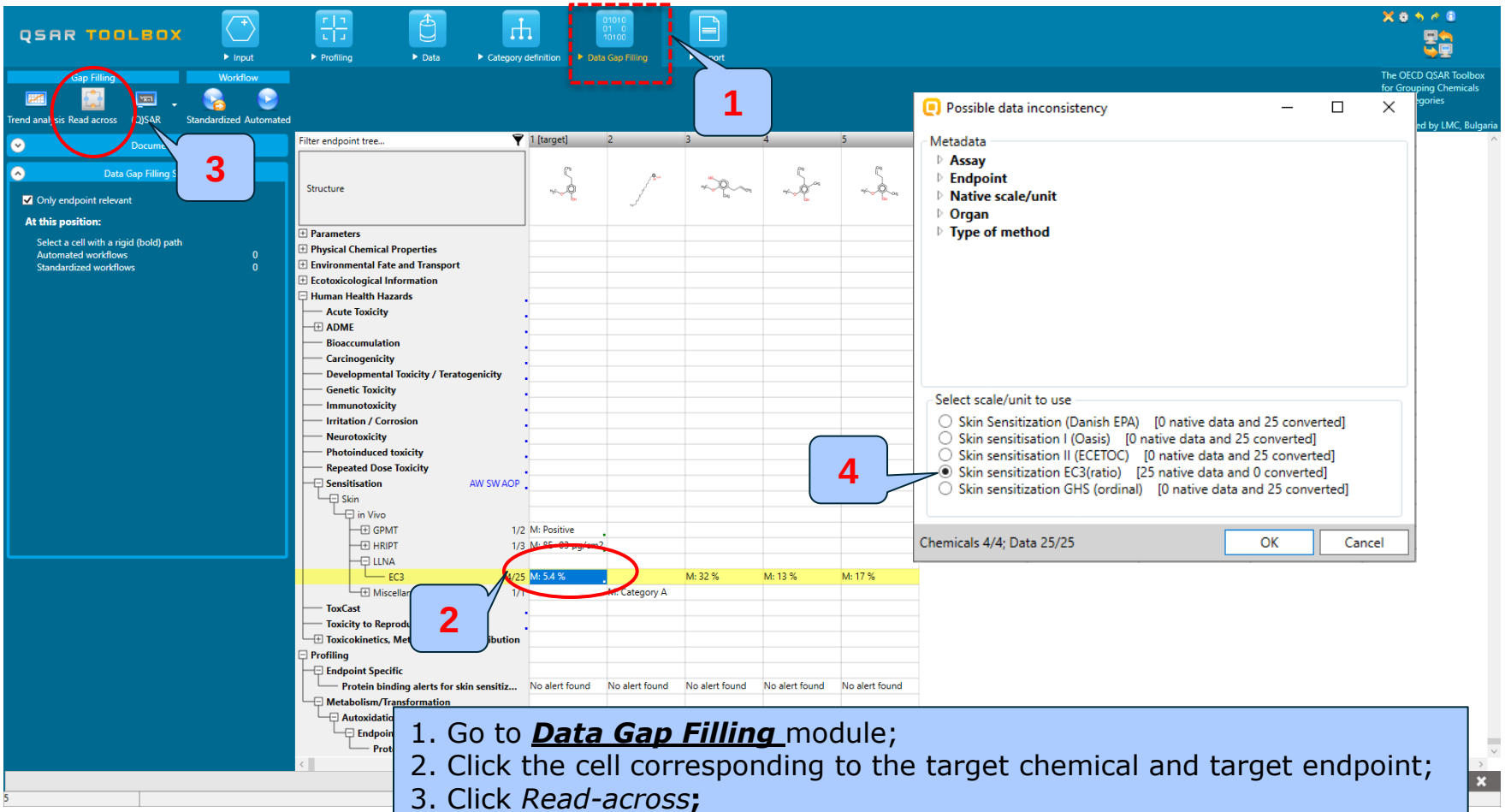
- In the current example we will use the potency scale - *Skin sensitization EC3(ratio)* scale in order to see the final prediction in percentage (%).

- The analogues will be checked for presence of additional protein binding alerts in their parent structures or after activation. The following subcategorizations will be applied for the purpose:

  - *Protein binding alerts for skin sensitization by OASIS*

  - *Protein binding alerts for skin sensitization by OASIS* combined with *autoxidation simulator*

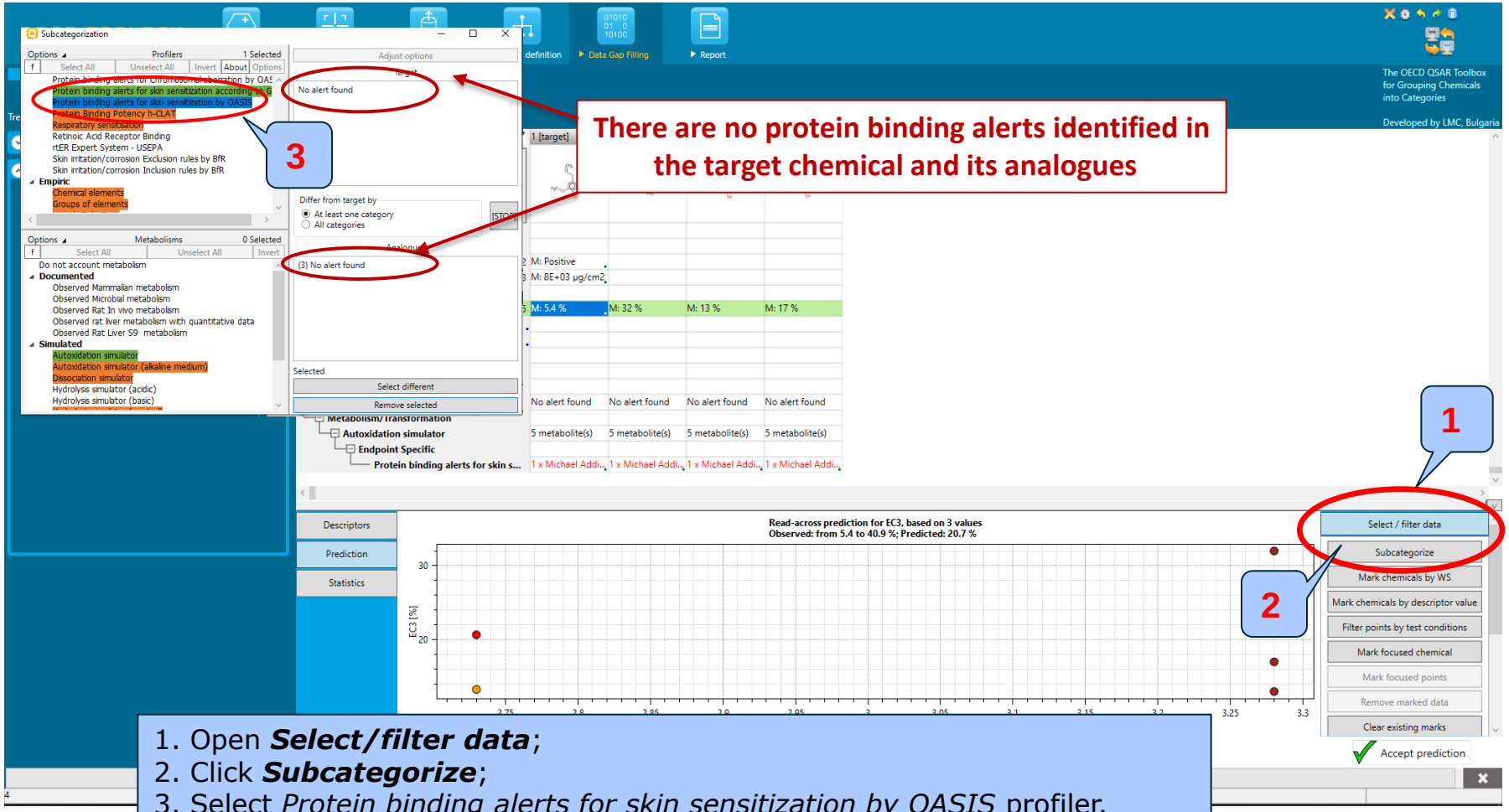
Data gap filling
Apply Read across



1. Go to ***Data Gap Filling*** module;
2. Click the cell corresponding to the target chemical and target endpoint;
3. Click *Read-across*;
4. Stay with the scale Skin sensitization EC3 (ratio). Click **OK**.

Data gap filling

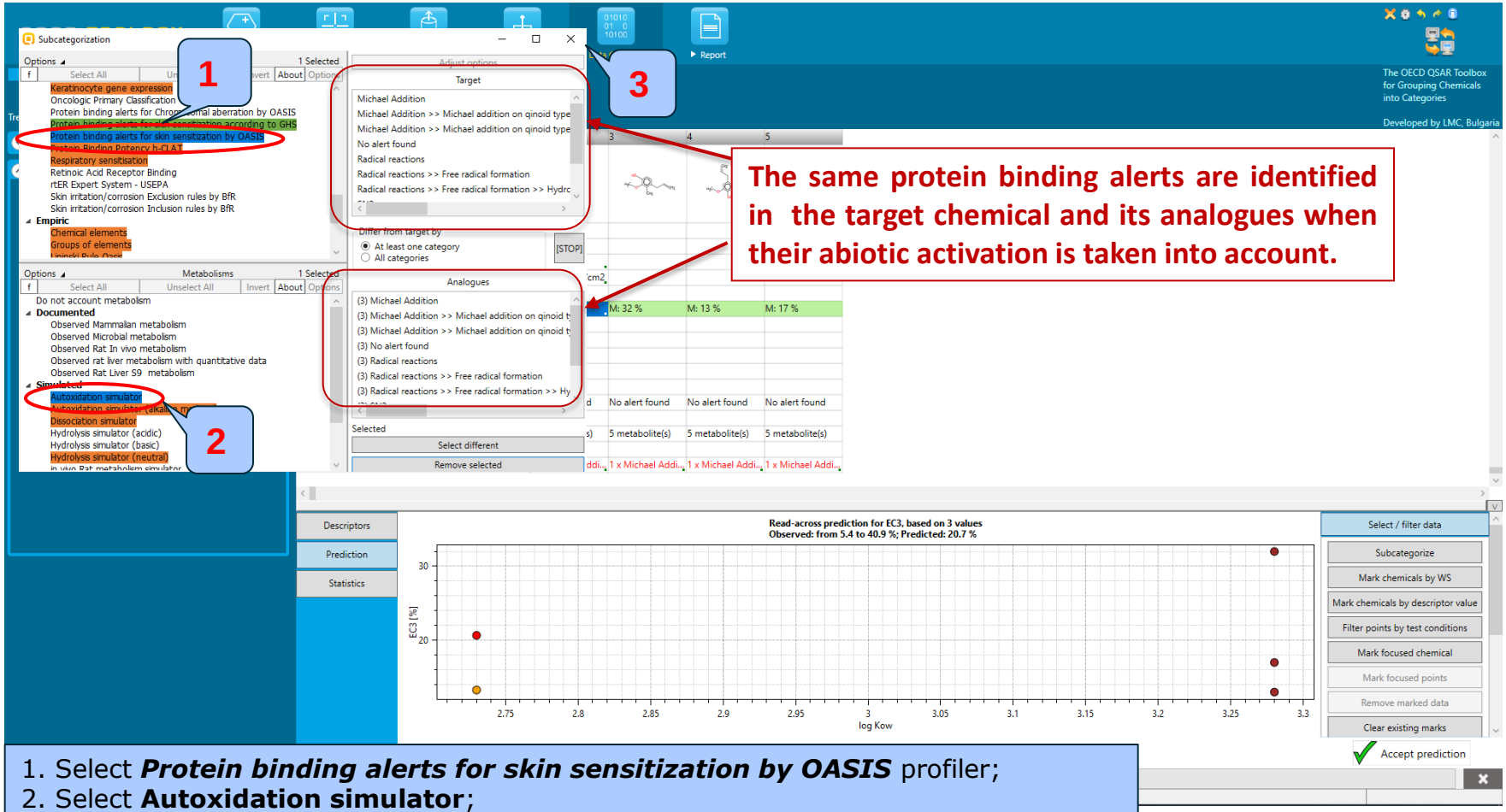
Subcategorization 1: Protein binding alerts for skin sensitization by OASIS



1. Open ***Select/filter data***;
2. Click ***Subcategorize***;
3. Select *Protein binding alerts for skin sensitization by OASIS* profiler.

Data gap filling

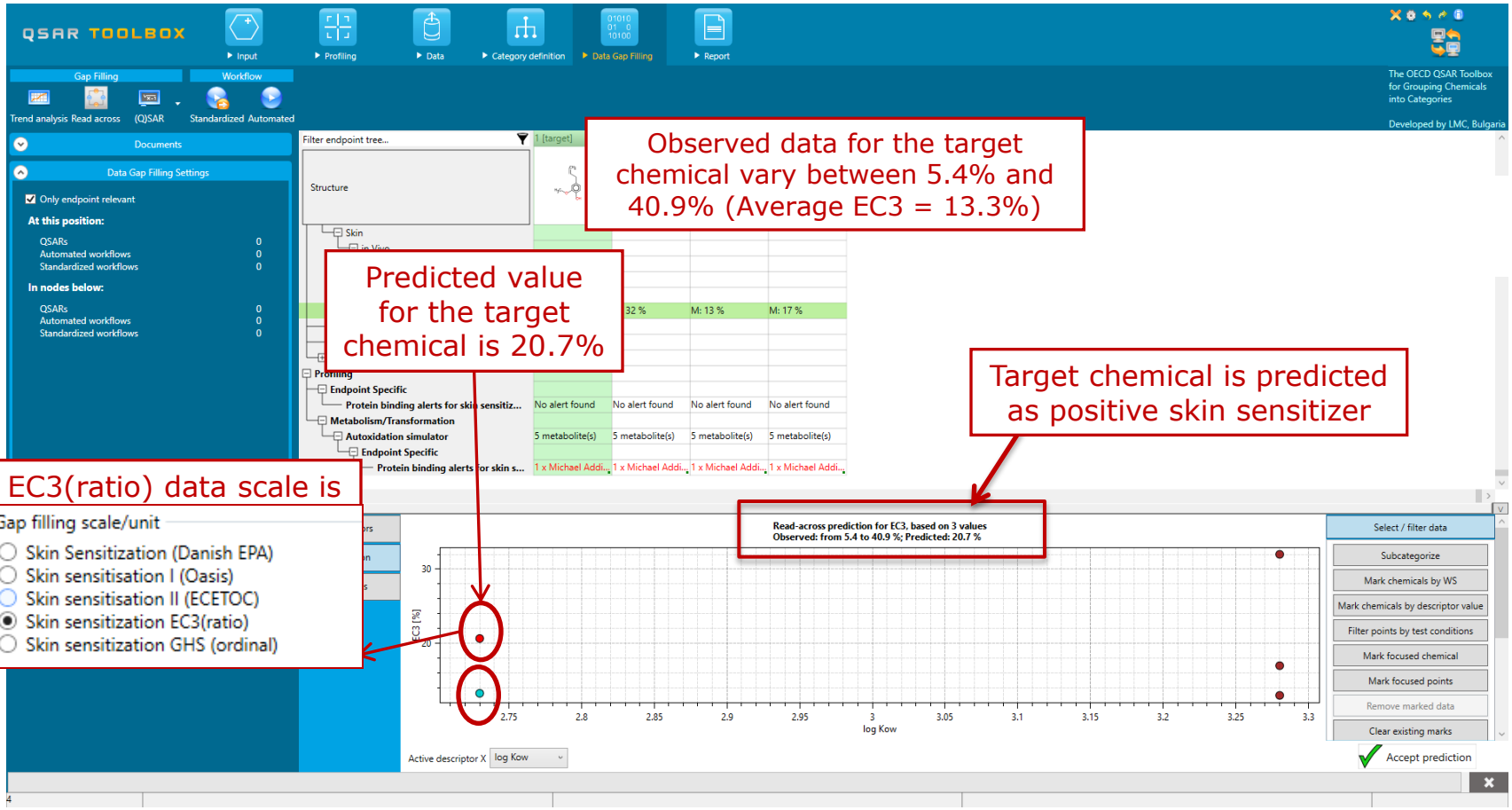
Subcategorization 2: Protein binding alerts for skin sensitization by OASIS combined with Autoxidation simulator



1. Select ***Protein binding alerts for skin sensitization by OASIS*** profiler;
2. Select **Autoxidation simulator**;
3. Close the *Subcategorization* window.

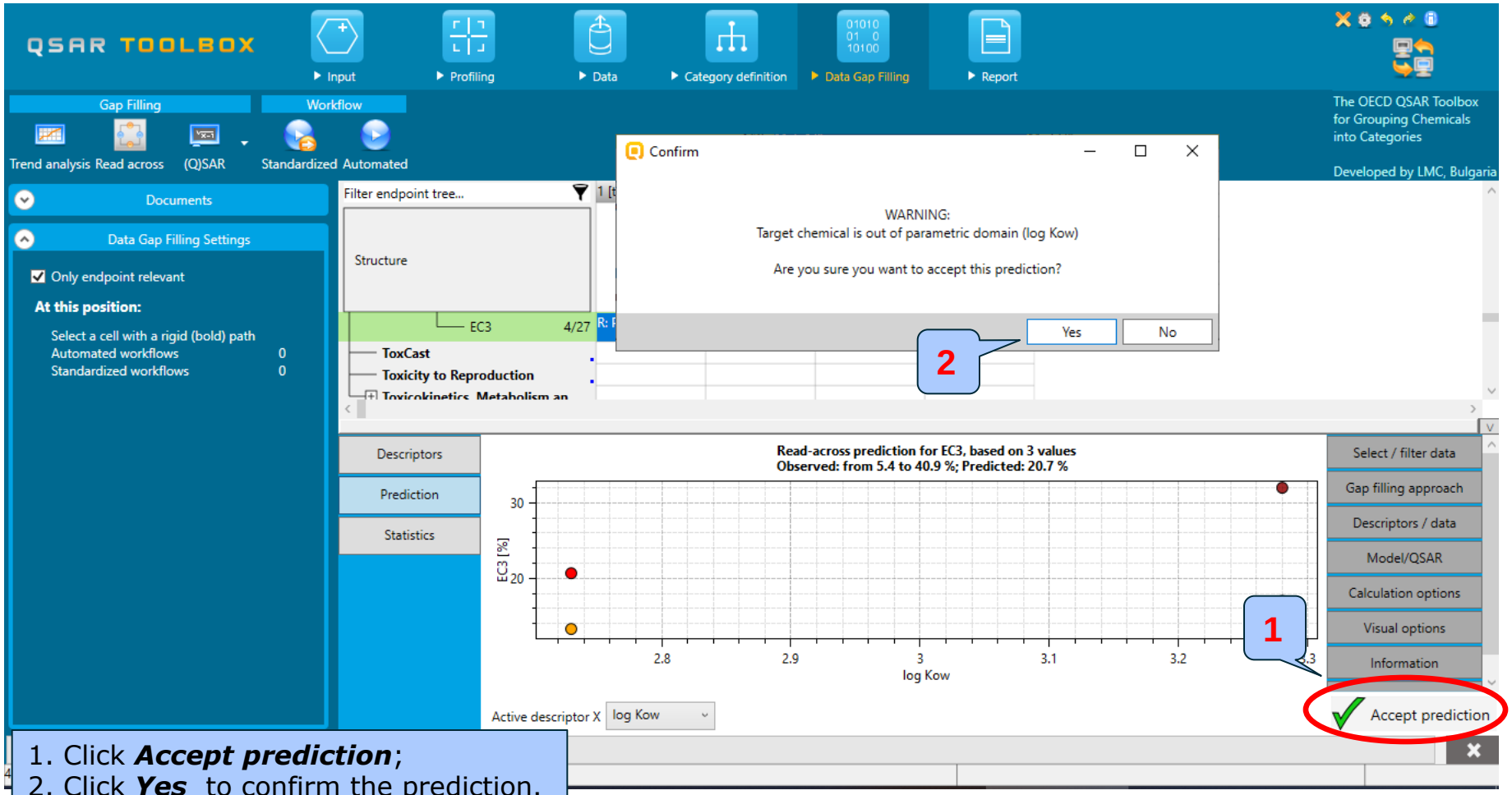
Data gap filling

Prediction for Skin sensitization, EC3: Overview



Data gap filling

Prediction for Skin sensitization, EC3: Acceptance

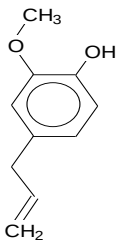


1. Click ***Accept prediction***;
2. Click ***Yes*** to confirm the prediction.

Recap

Parent

Eugenol
CAS# 97-93-0



Protein binding alert in the parent
(Protein binding by OASIS)

No alert found

Experimental data

LLNA Strong sensitizer

Categorization

Organic functional groups

Data gap filling

No protein binding alerts
Positive RA prediction

How to explain positive RA ?

Metabolites

5 autoxidation products

Protein binding alert in the metabolites
(Protein binding by OASIS + Autoxidation simulator)

Protein binding alerts identified in the package of metabolites

Categorization with metabolism

Identifying analogues of the target taking into account its metabolic activation

Data gap filling

Protein binding alerts identified

Positive RA prediction

Outlook

- Background
- Keywords
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Data
  - Categorization
  - Data gap filling
  - **Report**

Report
Overview

- The Report module allows you to generate a report on the predictions performed within the Toolbox.
- This module contains a predefined report template with automatically populated sections as well as manually editable sections, where the users could add some additional/custom information.
- The Prediction report generates three files:

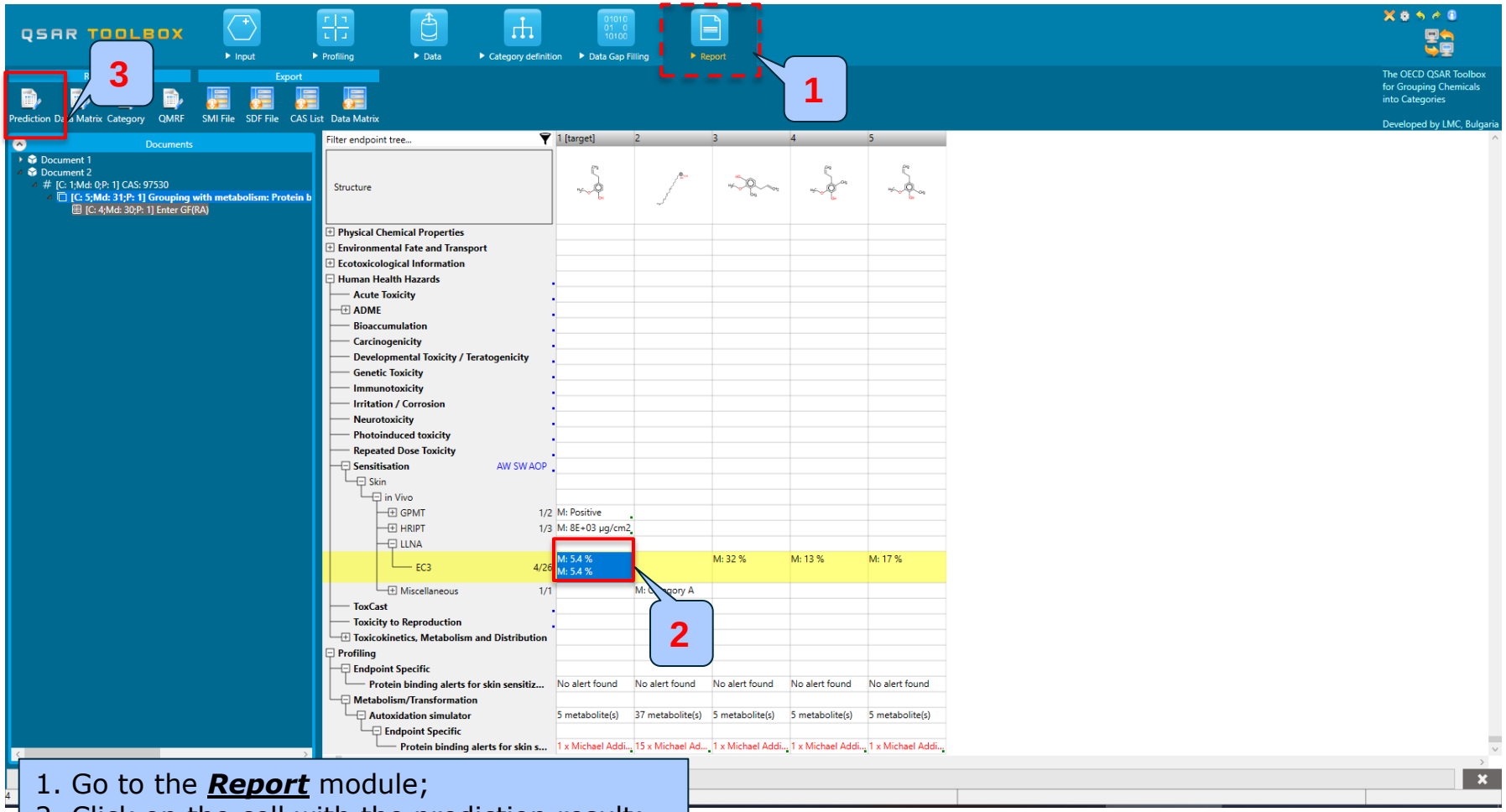
  - *Prediction report* - a PDF file containing information for the target and how the prediction is obtained.

  - *Category report* - a PDF file containing information for the consistency of the final category (target plus used analogues)

  - *Data matrix* - a MS Excel file containing chemicals used for prediction along with their data for selected parameters, profiles and endpoint tree positions.

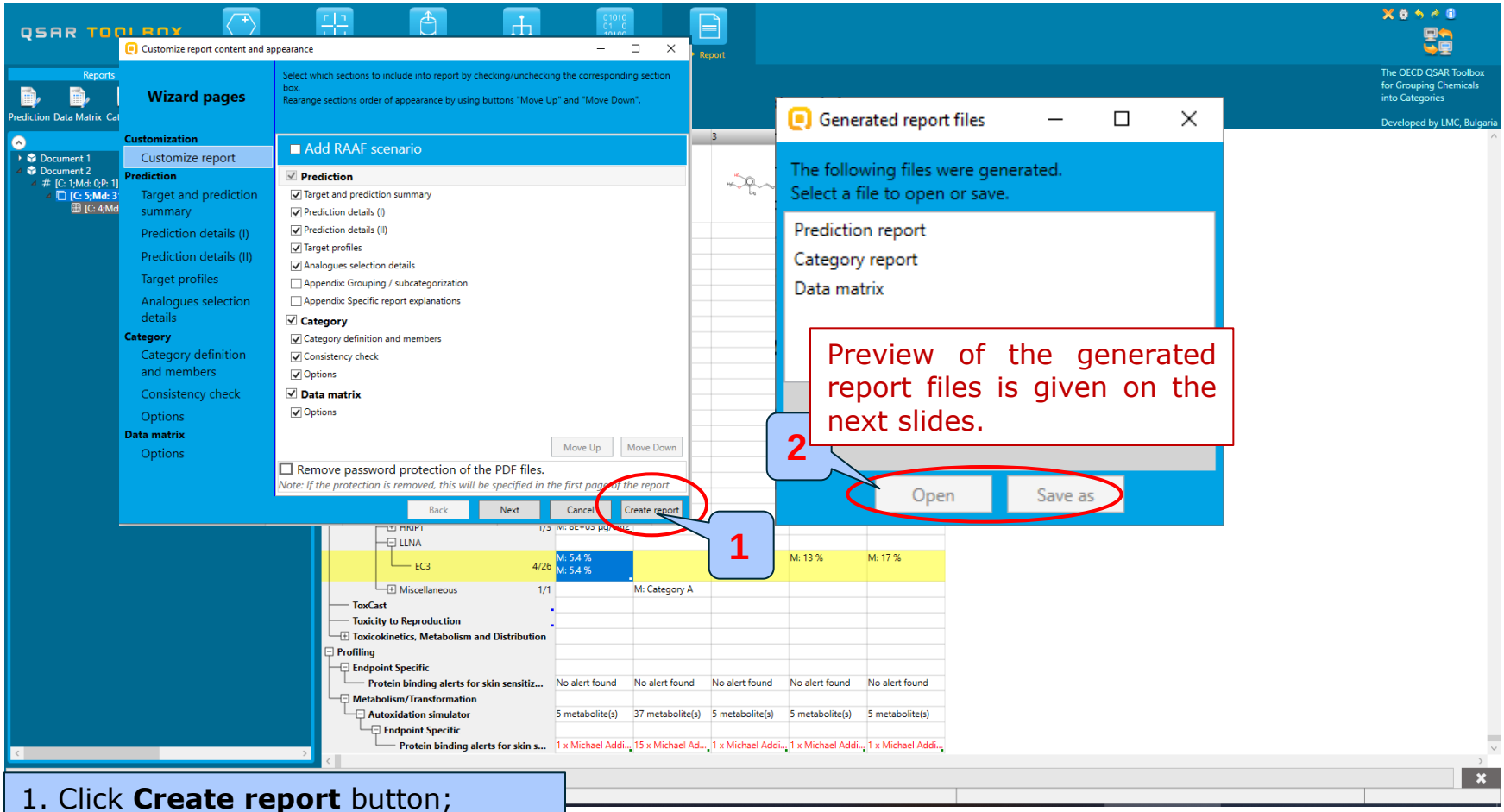
- The generated reports can then be saved or just opened.

Report



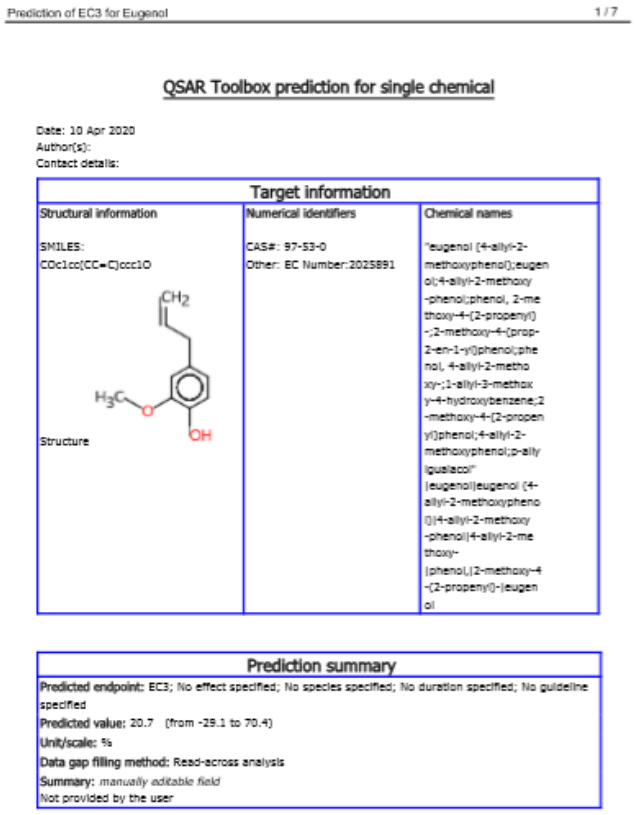
1. Go to the ***Report*** module;
2. Click on the cell with the prediction result;
3. Click ***Prediction***.

Report



1. Click **Create report** button;
2. Open and/or Save the files

Report
Prediction report



Prediction of EC3 for Eugenol 1 / 7

QSAR Toolbox prediction for single chemical

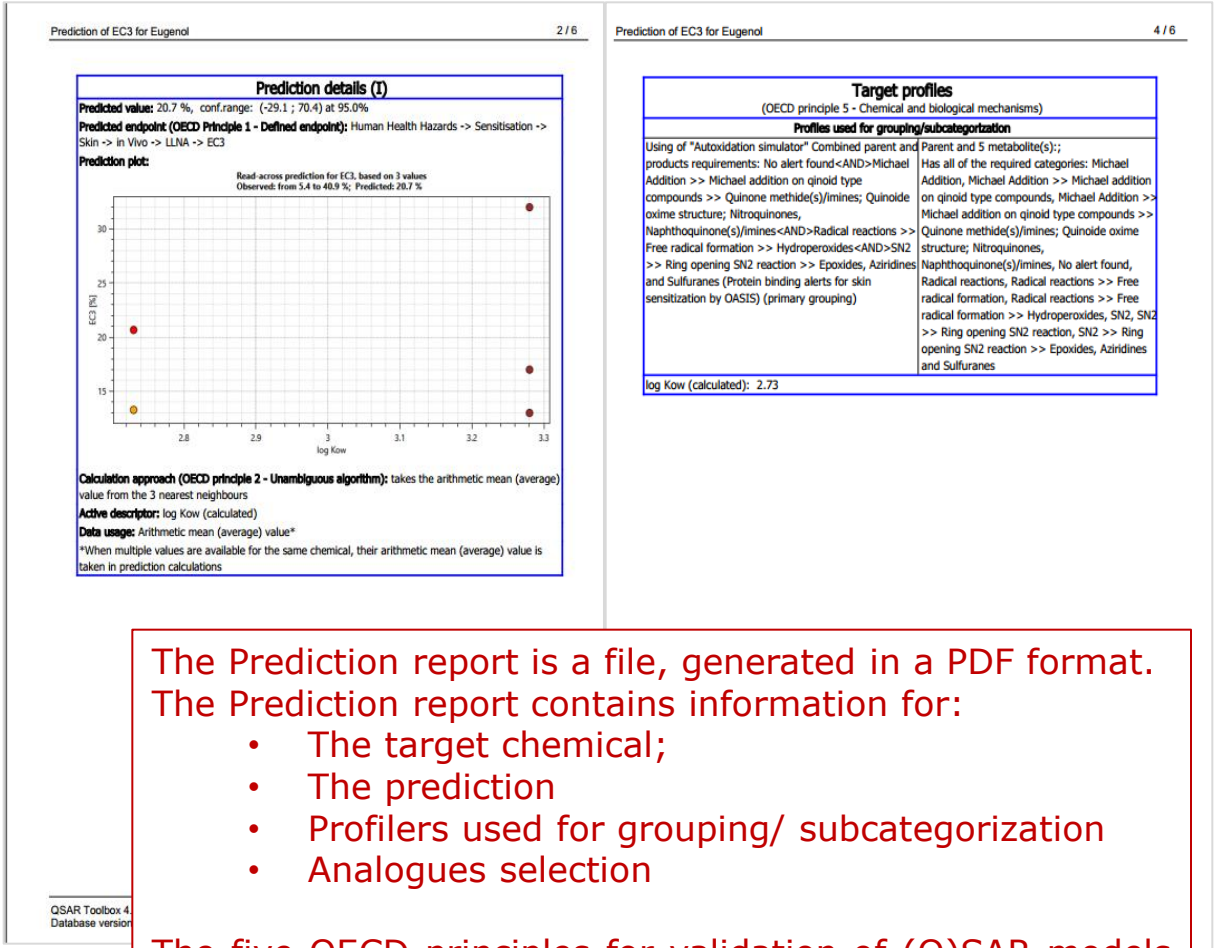
Date: 10 Apr 2020
Author(s):
Contact details:

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: COc1cc(CC=C)ccc1O Structure	CAS#: 97-53-0 Other: EC Number:202-589-1	"eugenol (4-allyl-2-methoxyphenol);eugenol;4-allyl-2-methoxy-phenol;phenol, 2-methoxy-4-(2-propenyl)-;2-methoxy-4-(prop-2-en-1-yl)phenol;phenol, 4-allyl-2-methoxy-;1-allyl-3-methoxy-4-hydroxybenzene;2-methoxy-4-[2-propenyl]phenol;4-allyl-2-methoxyphenol;p-allylguaiacol" |eugenol|eugenol (4-allyl-2-methoxyphenol)|4-allyl-2-methoxy-phenol|4-allyl-2-methoxy-|phenol,|2-methoxy-4-(2-propenyl)-|eugenol

Prediction summary

Predicted endpoint: EC3; No effect specified; No species specified; No duration specified; No guideline specified
Predicted value: 20.7 (from -29.1 to 70.4)
Unit/scale: %
Data gap filling method: Read-across analysis
Summary: *manually editable field*
Not provided by the user



Prediction of EC3 for Eugenol 2 / 6

Prediction details (I)

Predicted value: 20.7 %, conf.range: (-29.1 ; 70.4) at 95.0%
Predicted endpoint (OECD Principle 1 - Defined endpoint): Human Health Hazards -> Sensitisation -> Skin -> In Vivo -> LLNA -> EC3
Prediction plot:

Calculation approach (OECD principle 2 - Unambiguous algorithm): takes the arithmetic mean (average) value from the 3 nearest neighbours
Active descriptor: log Kow (calculated)
Data usage: Arithmetic mean (average) value*
*When multiple values are available for the same chemical, their arithmetic mean (average) value is taken in prediction calculations

QSAR Toolbox 4.
Database version

Prediction of EC3 for Eugenol 4 / 6

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

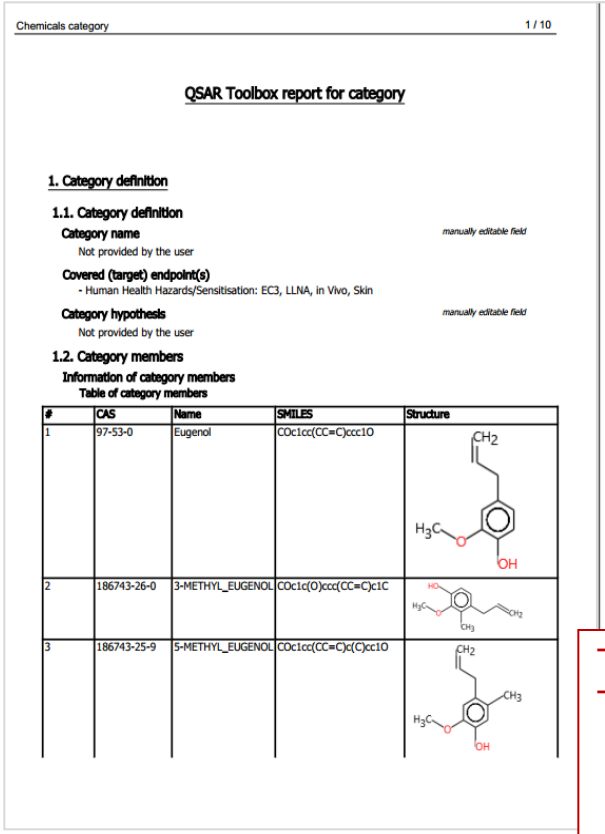
Profiles used for grouping/subcategorization	
Using of "Autoxidation simulator" Combined parent and products requirements: No alert found<AND>Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones, Naphthoquinone(s)/imines<AND>Radical reactions >> Free radical formation >> Hydroperoxides<AND>SN2 >> Ring opening SN2 reaction >> Epoxides, Aziridines and Sulfuranes (Protein binding alerts for skin sensitization by OASIS) (primary grouping)	Parent and 5 metabolite(s):; Has all of the required categories: Michael Addition, Michael Addition >> Michael addition on qinoid type compounds, Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones, Naphthoquinone(s)/imines, No alert found, Radical reactions, Radical reactions >> Free radical formation, Radical reactions >> Free radical formation >> Hydroperoxides, SN2, SN2 >> Ring opening SN2 reaction, SN2 >> Ring opening SN2 reaction >> Epoxides, Aziridines and Sulfuranes
log Kow (calculated): 2.73	

The Prediction report is a file, generated in a PDF format.
The Prediction report contains information for:

- The target chemical;
- The prediction
- Profilers used for grouping/ subcategorization
- Analogues selection

The five OECD principles for validation of (Q)SAR models are also given in the report.

Report
Category report


Chemicals category 1 / 10

QSAR Toolbox report for category

1. Category definition

1.1. Category definition

Category name *manually editable field*

Not provided by the user

Covered (target) endpoint(s)

- Human Health Hazards/Sensitisation: EC3, LLNA, in Vivo, Skin

Category hypothesis *manually editable field*

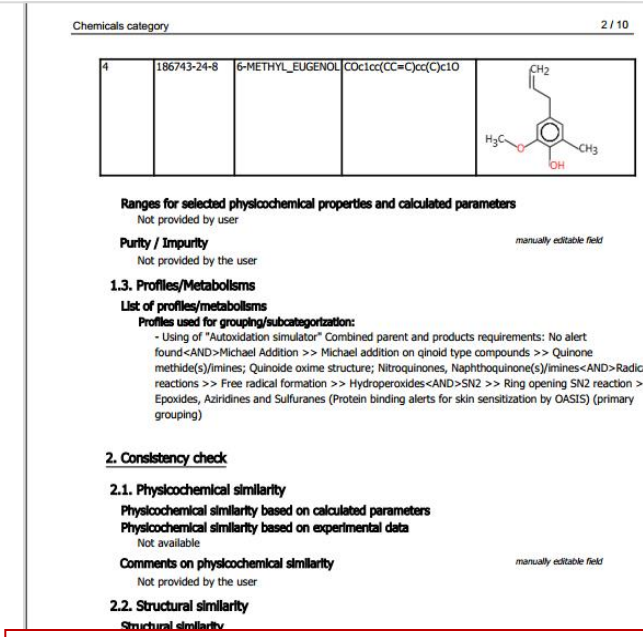
Not provided by the user

1.2. Category members

Information of category members

Table of category members

#	CAS	Name	SMILES	Structure
1	97-53-0	Eugenol	COc1cc(CC=C)ccc1O	
2	186743-26-0	3-METHYL_EUGENOL	COc1c(O)ccc(CC=C)c1C	
3	186743-25-9	5-METHYL_EUGENOL	COc1cc(CC=C)c(C)cc1O	


Chemicals category 2 / 10

4	186743-24-8	6-METHYL_EUGENOL	COc1cc(CC=C)cc(C)c1O	

Ranges for selected physicochemical properties and calculated parameters

Not provided by user

Purity / Impurity *manually editable field*

Not provided by the user

1.3. Profiles/Metabolisms

List of profiles/metabolisms

Profiles used for grouping/subcategorization:

- Using of "Autoxidation simulator" Combined parent and products requirements: No alert found<AND>Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones, Naphthoquinone(s)/imines<AND>Radical reactions >> Free radical formation >> Hydroperoxides<AND>SN2 >> Ring opening SN2 reaction >> Epoxides, Aziridines and Sulfuranes (Protein binding alerts for skin sensitization by OASIS) (primary grouping)

2. Consistency check

2.1. Physicochemical similarity

Physicochemical similarity based on calculated parameters

Physicochemical similarity based on experimental data

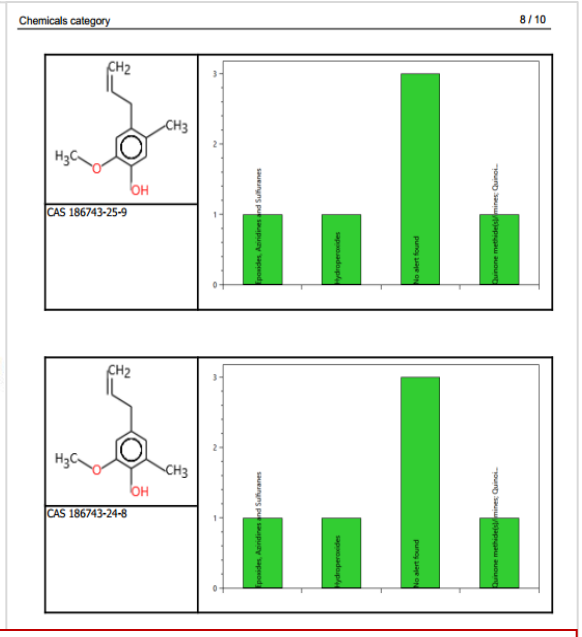
Not available

Comments on physicochemical similarity *manually editable field*

Not provided by the user

2.2. Structural similarity

Structural similarity



The Category report is a file, generated in a PDF format.

The Category report* contains information for:

- Category members (i.e. target and analogues used for the prediction);
- Physicochemical similarity between the category members
- Structural similarity between the category members
- Mechanistic similarity between the category members
- Additional data related to the target endpoint

*__Note:__ In the current example some of the Category report sections will be empty. They will be automatically populated if the *Category elements* are preliminary applied. See more details in *Tutorial 27: Category elements for assessing Category consistency.*

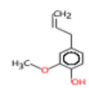
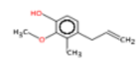
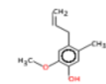
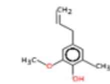
Report
Data matrix report

Substance ID information

Profiling information used for grouping/subcategorization

Experimental data used for the prediction

Additional experimental data

#	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1					Target chemical			Neighbour #1			Neighbour #2			Neighbour #3
2	Substance identity													
3	Structure													
4	CAS number				97-53-0			186743-26-0			186743-25-9			186743-24-8
5	Chemical name				Eugenol			3-METHYL_EUGENOL			5-METHYL_EUGENOL			6-METHYL_EUGENOL
6	Other identifier													
7	SMILES				COc1cc(CC=C)ccc1O			COc1c(O)ccc(CC=C)c1C			COc1cc(CC=C)c(C)cc1O			COc1cc(CC=C)cc(C)c1O
9	Parameters	unit												
10														
11	Profilers													
12	*Profiles used for grouping/subcategorization*													
13	Using of "Autoxidation simulator" Combined parent and products requirements: No alert found<AND>Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones, Naphthoquinone(s)/imines<AND>Radical reactions >> Free radical formation >> Hydroperoxides<AND>SN2 >> Ring opening SN2 reaction >> Epoxides, Aziridines and Sulfuranes (Protein binding alerts for skin sensitization by OASIS) (primary grouping)				Parent and 5 metabolite(s):; Has all of the required categories: Michael Addition, Michael Addition >> Michael addition on qinoid type compounds, Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones, Naphthoquinone(s)/imines, No alert found, Radical			Parent and 5 metabolite(s):; Has all of the required categories: Michael Addition, Michael Addition >> Michael addition on qinoid type compounds, Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones,			Parent and 5 metabolite(s):; Has all of the required categories: Michael Addition, Michael Addition >> Michael addition on qinoid type compounds, Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones,			Parent and 5 metabolite(s):; Has all of the required categories: Michael Addition, Michael Addition >> Michael addition on qinoid type compounds, Michael Addition >> Michael addition on qinoid type compounds >> Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones,
14	*Endpoint Specific*													
15	Protein binding alerts for skin sensitization by OASIS				No alert found			No alert found			No alert found			No alert found
17	Measured and predicted data													
18	*Data used for prediction*													
19	*sublevel*	*endpoint*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test guideline, year, reference*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test*
20	Sensitisation	EC3				32	%	mouse EC3 in Vivo	13	%	mouse EC3 in Vivo	17	%	mouse EC3 in Vivo
21	*Human Health Hazards#Sensitisation*													
22	*sublevel*	*endpoint*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test guideline, year, reference*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test*	*value*	*unit*	*species, duration, test type, type of method, assay, strain, test*
23	Sensitisation	CD54	Positive		CD54 in Vitro Dendritic Cell Activity (h-CLAT)									
24	Sensitisation	CD54	Positive		CD54 in Vitro Dendritic Cell Activity (h-CLAT)									
25	Sensitisation	CD86	Positive		CD86 in Vitro									

Sheet1

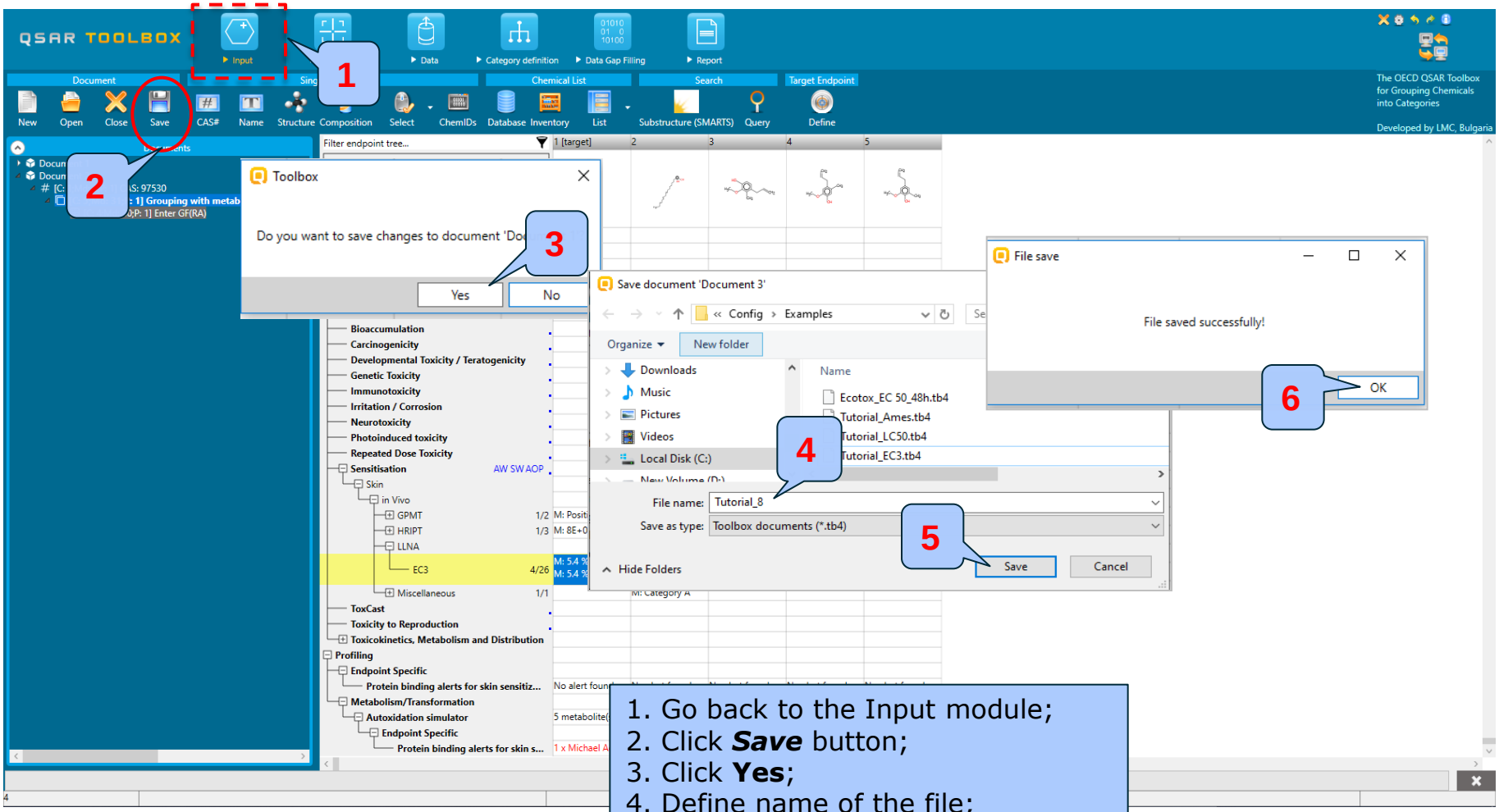
Outlook

- Background
- Keywords
- Objectives
- The exercise
- Workflow
- **Save/Load**

Saving the prediction result
Overview

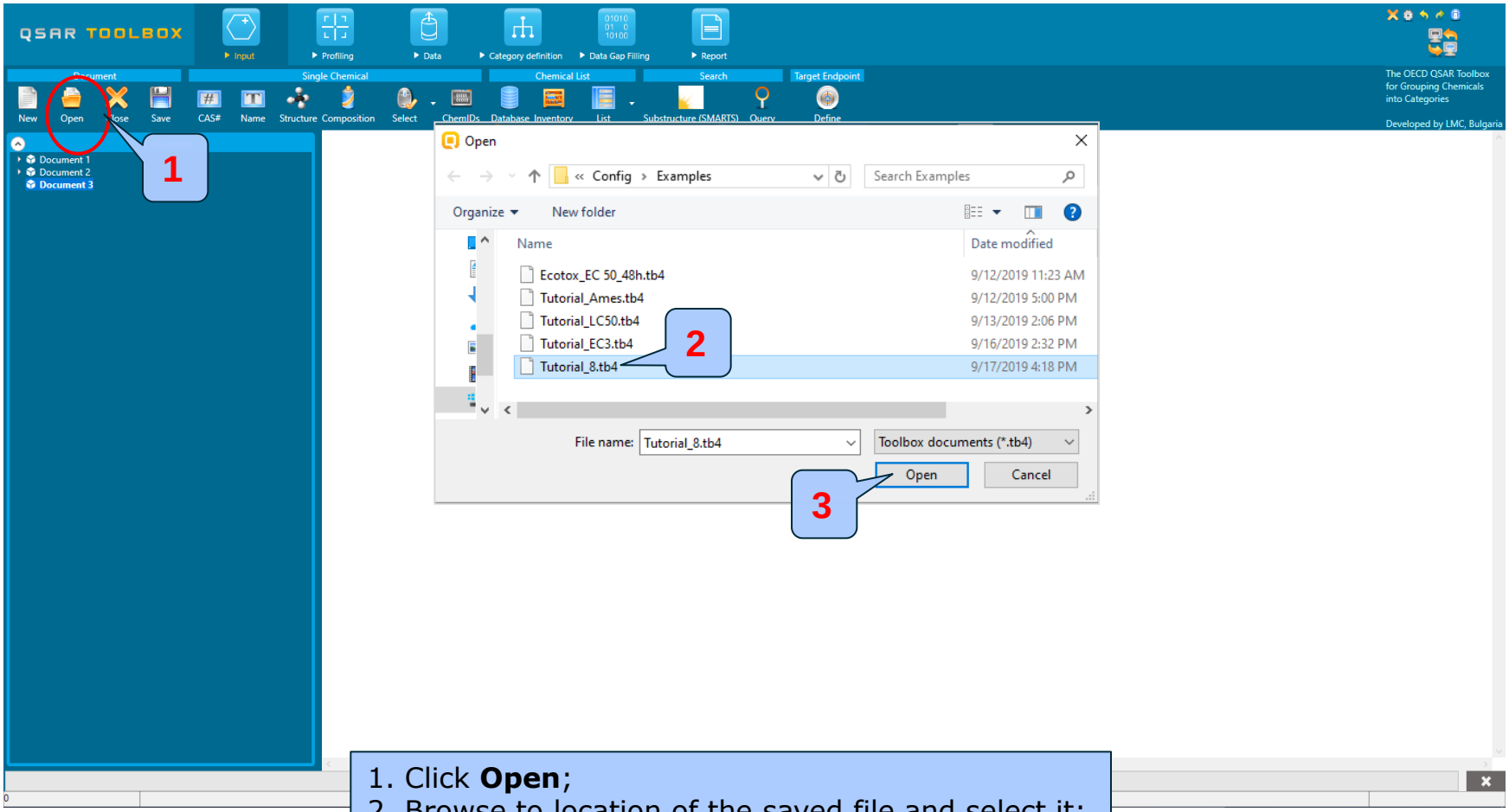
- The Save/Load functionalities allow storing/restoring of Toolbox documents including loaded chemicals, experimental data, profiles, predictions, etc.
- These functionalities are implemented based on saving the sequence of actions performed in a Toolbox document and later executing of these actions in the same sequence of steps in order to get the same result(s).
- Saving/Loading of a Toolbox file is shown on the next screenshots.

Saving the prediction result



1. Go back to the Input module;
2. Click ***Save*** button;
3. Click **Yes**;
4. Define name of the file;
5. Click on the **Save** button;
6. Click **OK**.

Open the saved file



1. Click **Open**;
2. Browse to location of the saved file and select it;
3. Click **Open**