QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

OECD QSAR Toolbox v.3.4

Predicting skin sensitisation potential of eugenol (CAS 97-53-0) using a new categorization tool taking into account its abiotic activation

Outlook

- **Background**
- Objectives
- The exercise
- Workflow

Background

- This is a step-by-step presentation designed to take the user through the Toolbox workflow for predicting skin sensitization potential of eugenol using a newly implemented categorization tool taking into account its abiotic activation.

Outlook

- Background
- **Objectives**
- The exercise
- Workflow

Objectives

This presentation demonstrates a number of functionalities of the Toolbox:

- Profiling the target chemical.
- Identifying analogues of the target chemical.
- Filling data gaps for target chemical by read-across.
- Profiling target chemical taking into account its (a)biotic activation.
- Identifying analogues of the target using a new categorization functionality allowing (a)biotic activation to be taken into account.
- Filling data gaps by read across when (a)biotic activation is taken into account.

Outlook

- Background
- Objectives
- **The exercise**
- Workflow

The Exercise

- In this exercise we will predict the skin sensitization potential of target chemical **Eugenol** [**CAS# 97-53-0**].
- Profile and gather data for the target chemical.
- Two types categorizations are applied:
  - Identifying analogues using well-known categorization group
  - Identifying analogues based on autoxidation activation of the target illustrating new categorization functionality
- Filling data gap by read-across.

Outlook

- Background
- Objectives
- The exercise
- **Workflow**

Workflow

- **As you know the Toolbox has 6 modules which are typically used in sequence:**
  - Chemical Input
  - Profiling
  - Endpoint
  - 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
- Objectives
- The exercise
- **Workflow**
  - **Input**

Chemical 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.

Chemical Input
Ways of Entering a Chemicals

User Alternatives for input of Chemical:

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
- Chemical IDs such as EC number, ENECS number

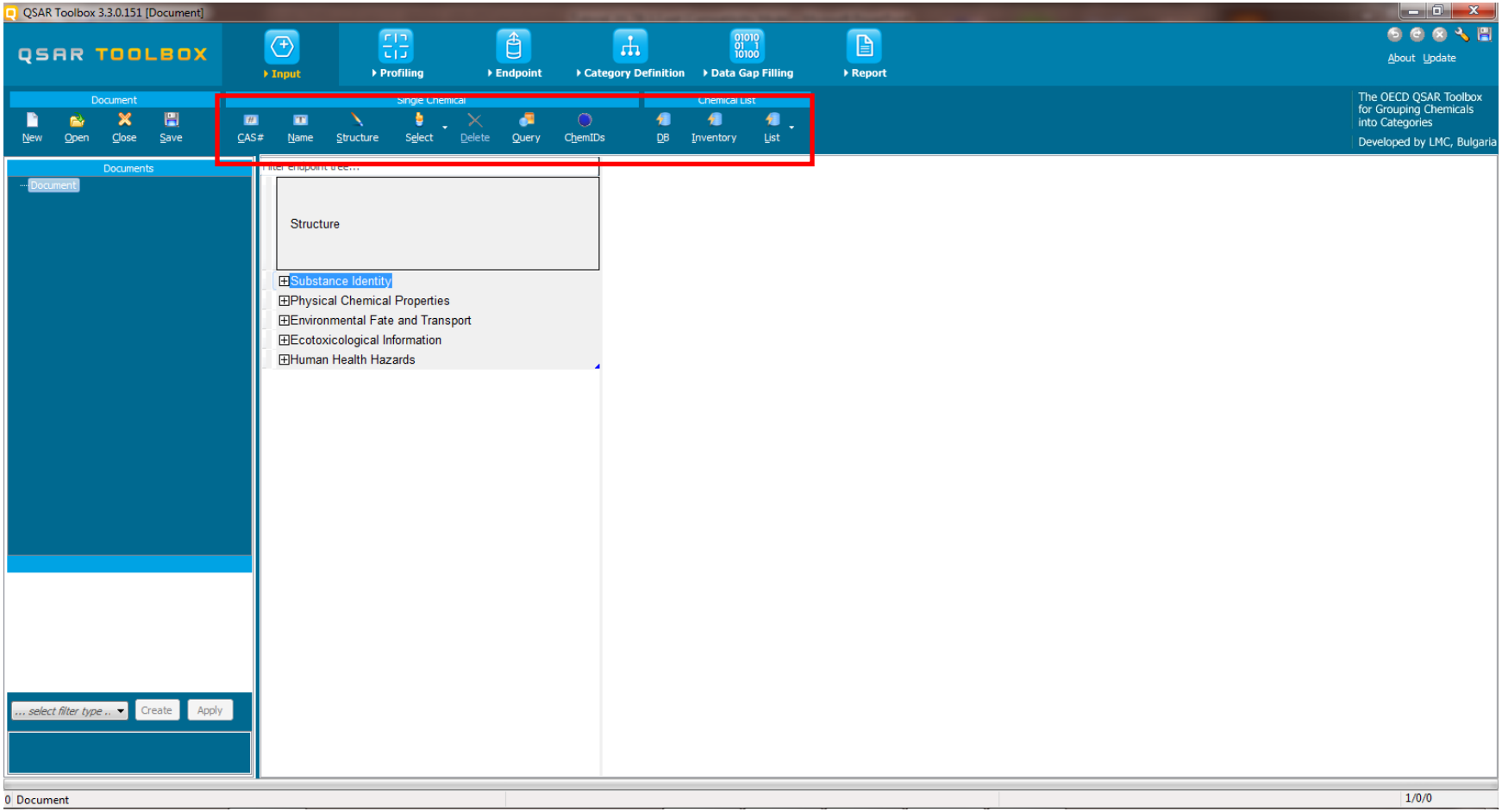
B. Group of chemicals

- User List/Inventory
- Specialized Databases

Chemical Input
Input Screen

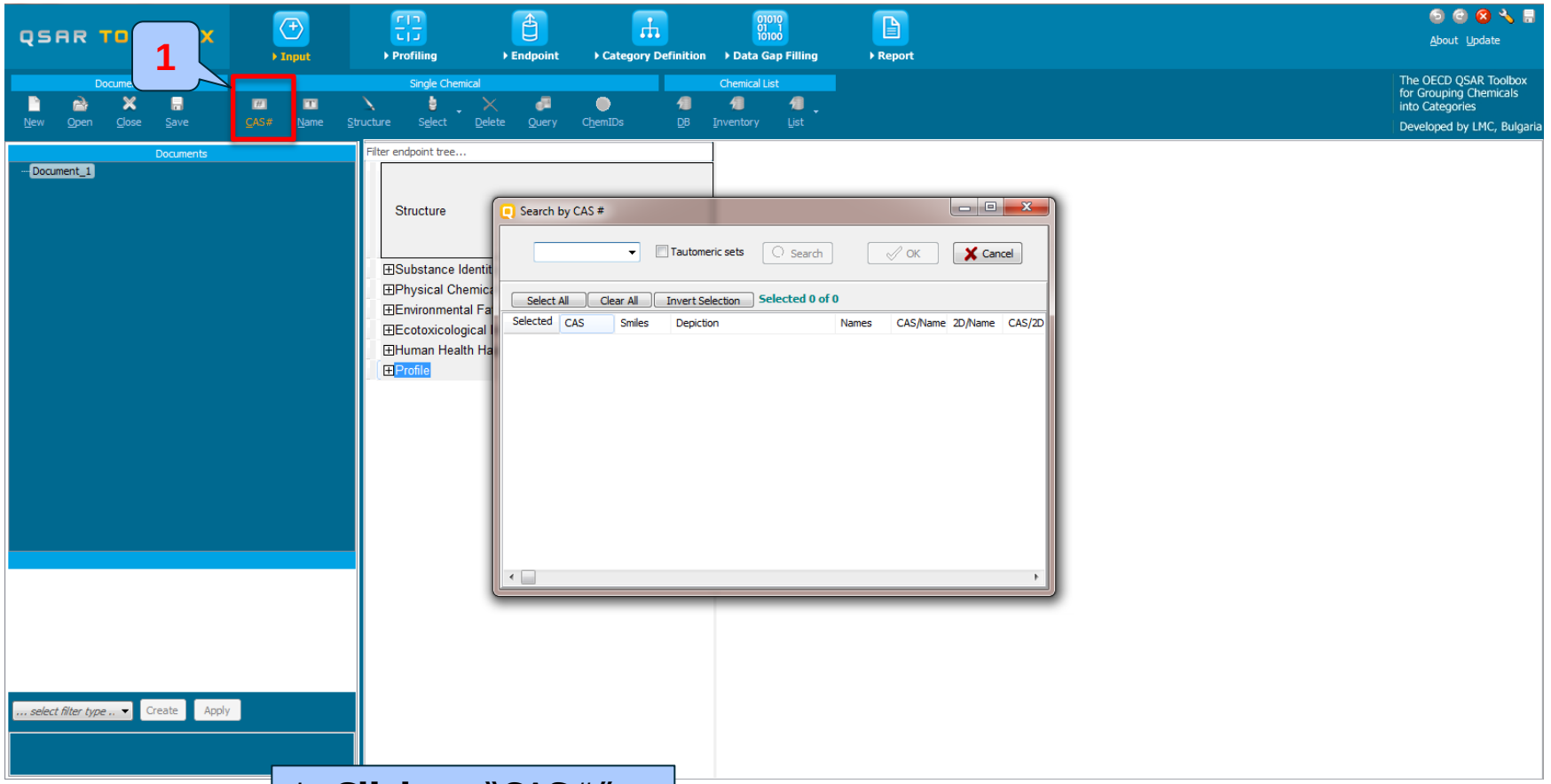
- Open the Toolbox.
- The six modules in the workflow are seen listed next to "QSAR TOOLBOX" title.
- Click on "Input" (see next screen shot)

Chemical Input
Input Screen



Chemical Input

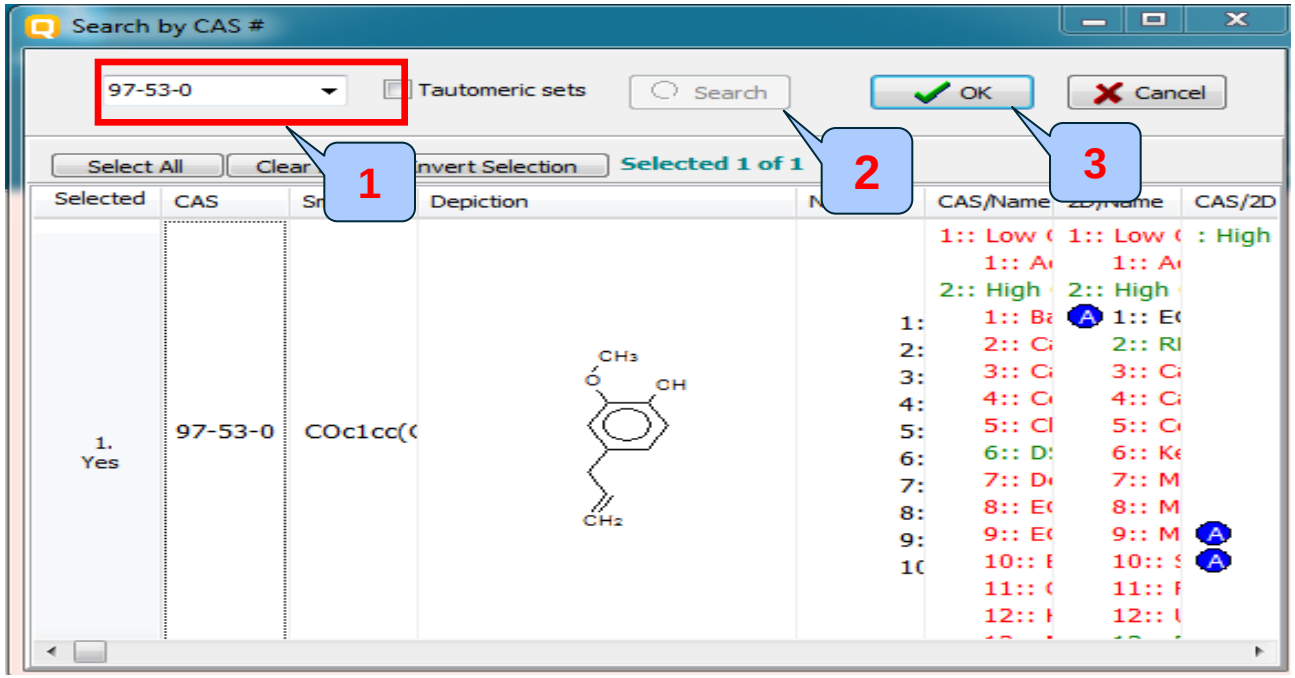
Input target chemical by CAS#



1. **Click** on "CAS#"

Chemical Input

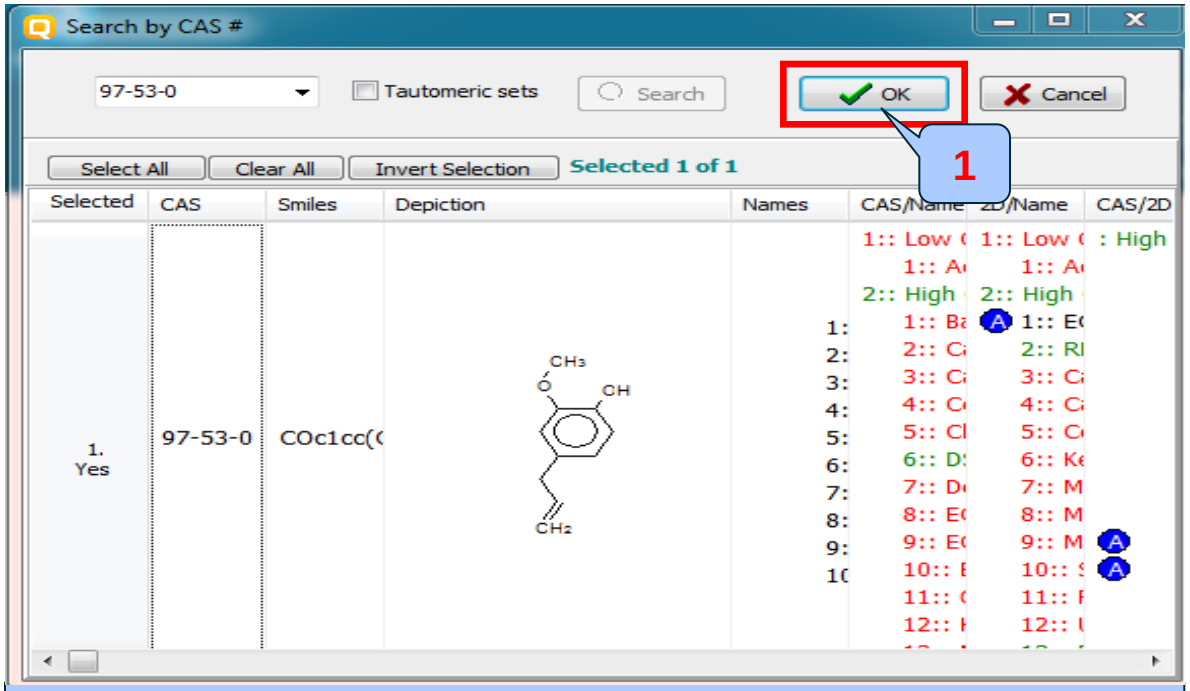
Enter CAS# of 2-methoxy-4-(2-propenyl)phenol (Eugenol)



1. **Enter** the CAS# in the blank field; 2. **Click** "Search" button; 3. **Press** "OK"

Chemical Input
Target chemical identity

The Toolbox now searches the databases to find out if the CAS# you entered is linked to a molecular structure stored in the Toolbox. It is displayed as a 2-demensional depiction.

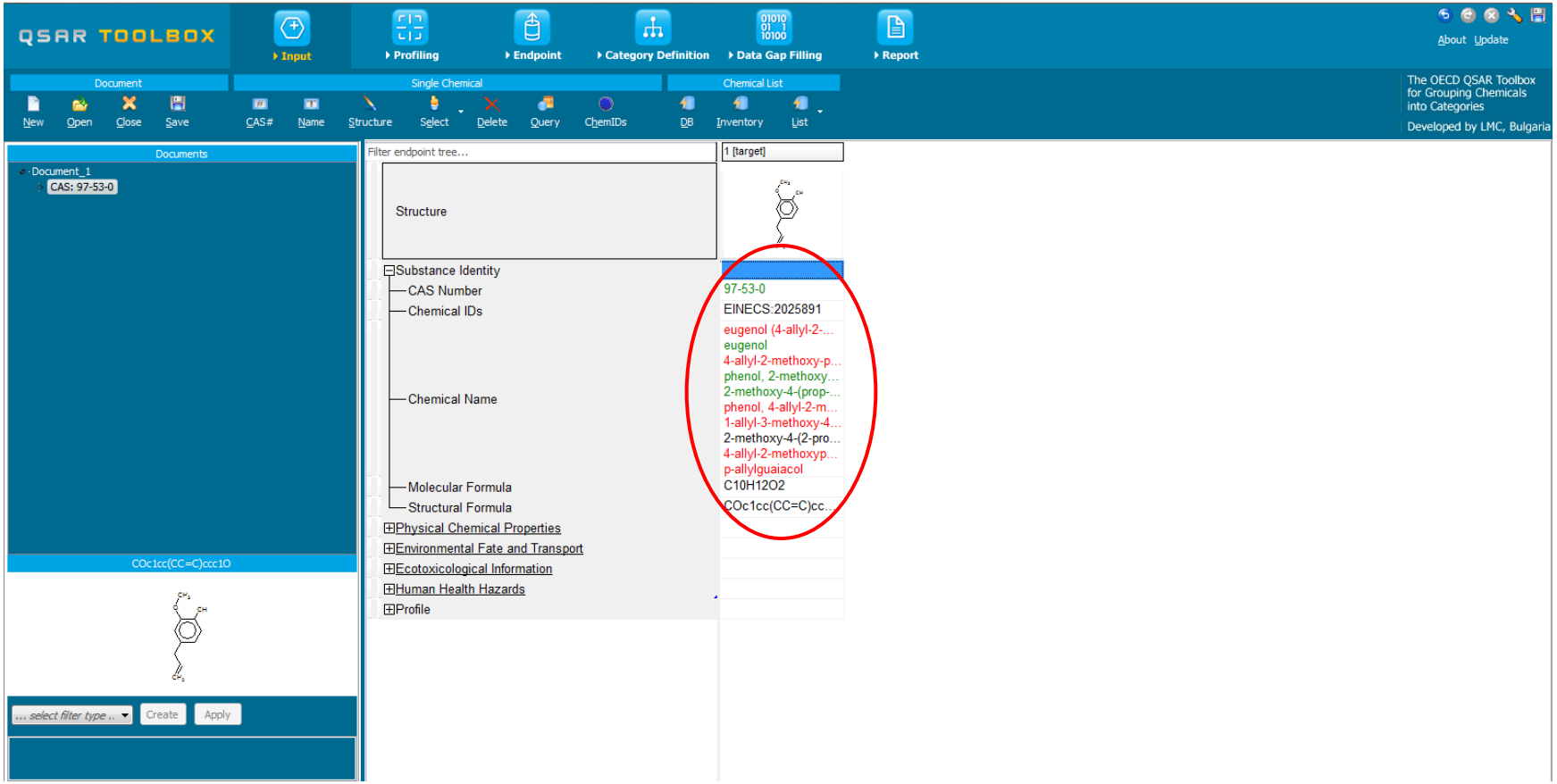


1. **Click** "OK" to enter the target structure into data matrix

Chemical Input
Target chemical identity

- Double click "Substance Identity" displays the chemical identification information.
- The user should note that existing names of the target chemical are presented in different colours. This indicates the reliability of relation CAS-Name-SMILES for the target chemical (see next screen shots).
- The workflow on the first module is now complete, and the user can proceed to the next module.

Chemical Input
Target chemical identity



Chemical Input
Target chemical identity

The colour code indicates the reliability of the chemical identifier:

- **Green**: There is a high reliability between the identifier and the structure. This colour is applied if the identifier is the same in several quality assured databases.
- **Yellow:** There is only a moderate reliability between the identifier and the structure. The colour is applied if the identifier is the same in several databases for which the quality assurance could not be established.
- **Red**: There is a poor reliability between the identifier and the structure. The colour is applied if the identifier is allocated to different structures in different databases.

Outlook

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

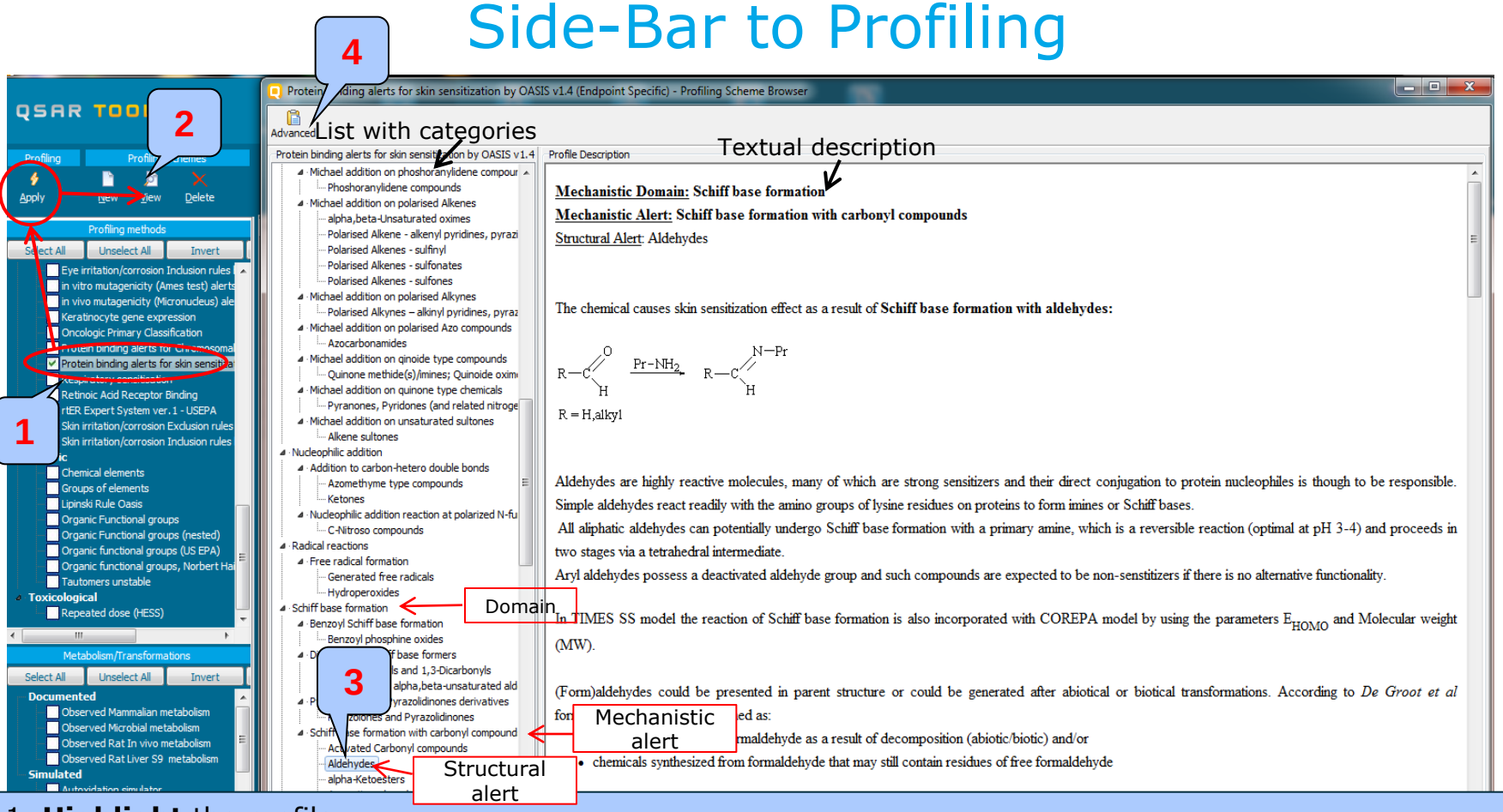
Profiling
Overview

- "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
Side-Bar to Profiling

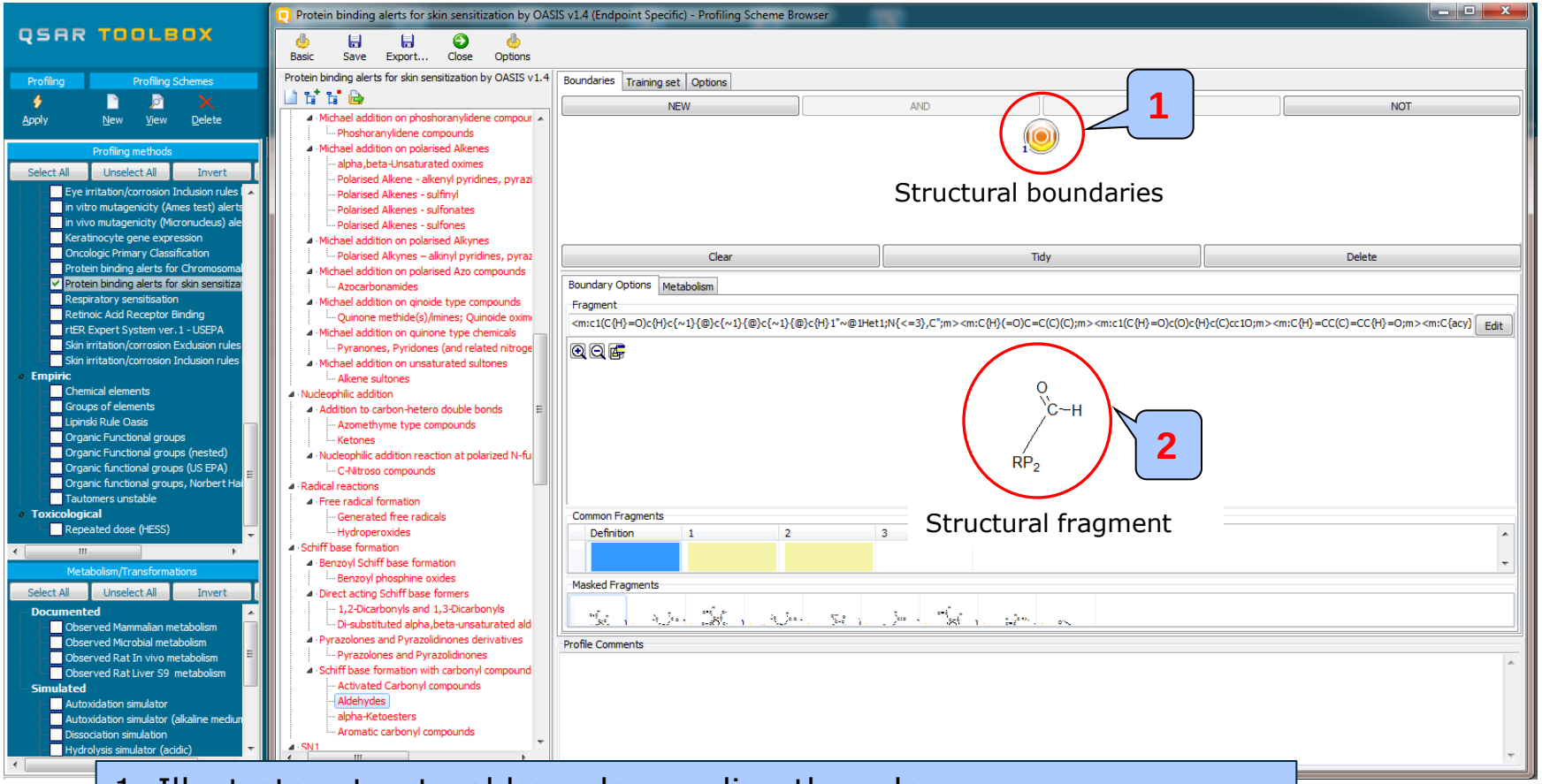
- For most of the profilers, background information can be retrieved by highlighting one of the profilers (for example, Protein binding alerts for skin sensitization by OASIS v1.4 and clicking on “View” (see next screen shot).

Profiling
Side-Bar to Profiling



1. **Highlight** the profiler
2. **Click** "View"
3. **Click** over "Aldehydes" to see textual description associated with the category. In order to see more details about structural boundaries coding the rule you should click "Advanced" button (4) (see next slide)

Profiling
Side-Bar to Profiling



1. Illustrates structural boundary coding the rule
2. Illustrates structural fragment used for defining the rule

Profiling
Profiling the target chemical

- The outcome of the profiling determines the most appropriate way to search for analogues (detailed information about profilers could be found in "Manual for Getting started" (Chapter 4) published on the OECD website:

  http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm

- Table 4 - 1 in chapter 4 (Manual for getting started) lists a selection of profilers and their relevance for different endpoints of regulatory relevance.

- The following profiling schemes are relevant to the **Skin sensitization**:
  - Protein binding by OECD – general mechanistic
  - Protein Binding Potency – general mechanistic
  - Protein binding alerts for skin sensitization by OASIS v1.4 – endpoint specific

Profiling
Profiling the target chemical

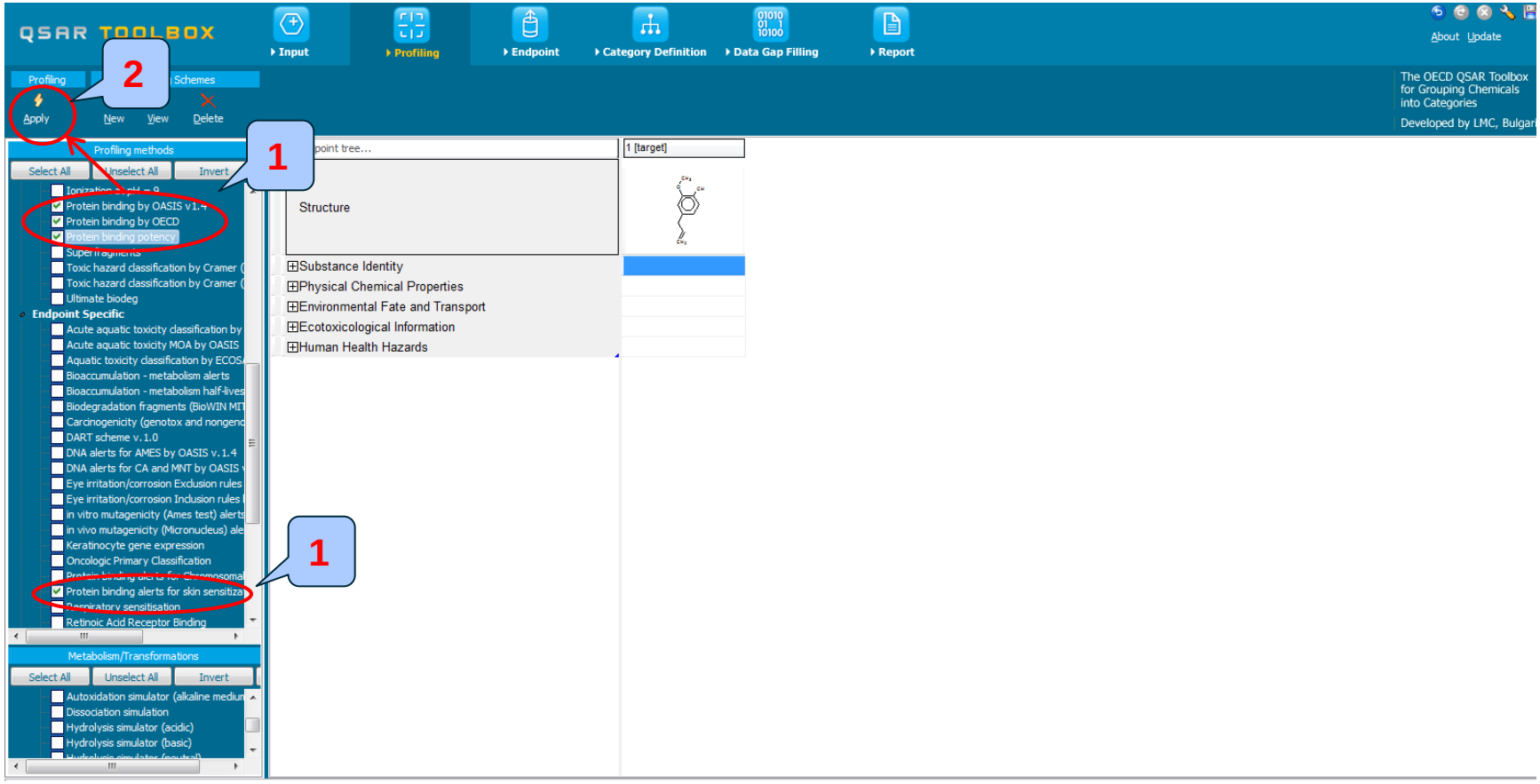
- **Click** in the box next to the name of the profiling methods related to the target endpoint.

- This selects (a **green** check mark appears) or deselects (**green** check mark disappears) profilers.

- For this example, go through the general and endpoint specific profiling mechanisms and highlight those that are relevant to skin sensitization effect (see next screen shot).

Profiling

Profiling the target chemical



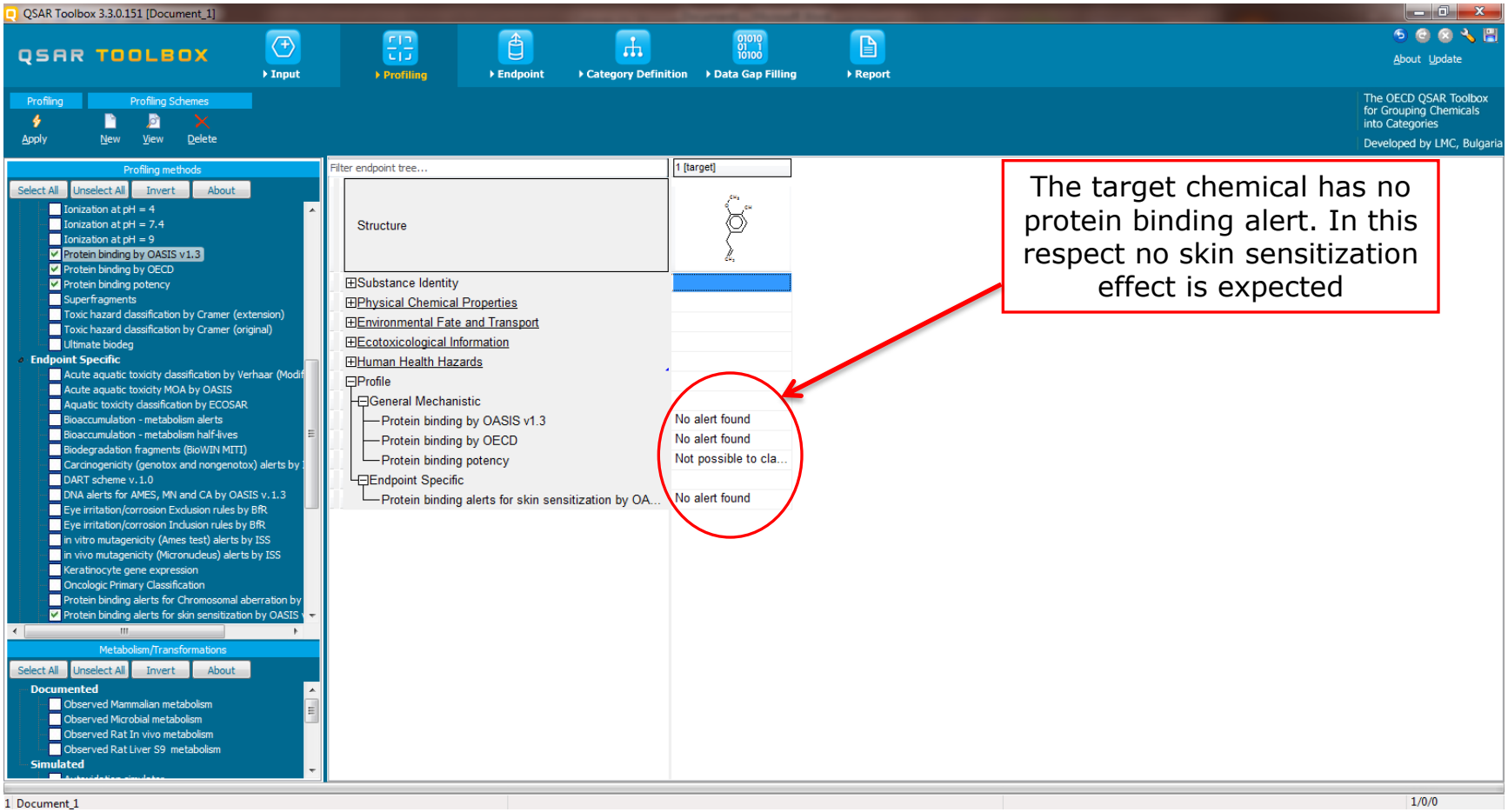
1. **Select** protein binding profiles from "**General Mechanistic**" and "**Endpoint specific**" group mentioned on slide 26
2. **Click** "Apply"

Profiling
Profiling the target chemical

- The actual profiling will take up to several seconds depending on the number and type of profilers selected.
- The results of profiling automatically appear as a dropdown box under the target chemical (see next screen shot).
- Please note the result obtained by the specific protein-binding profilers.
- No protein binding alert has been found for the target compound (eugenol) based on three protein binding profilers. Therefore no skin sensitization effect is expected.

Profiling

Profiling the target chemical



Outlook

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

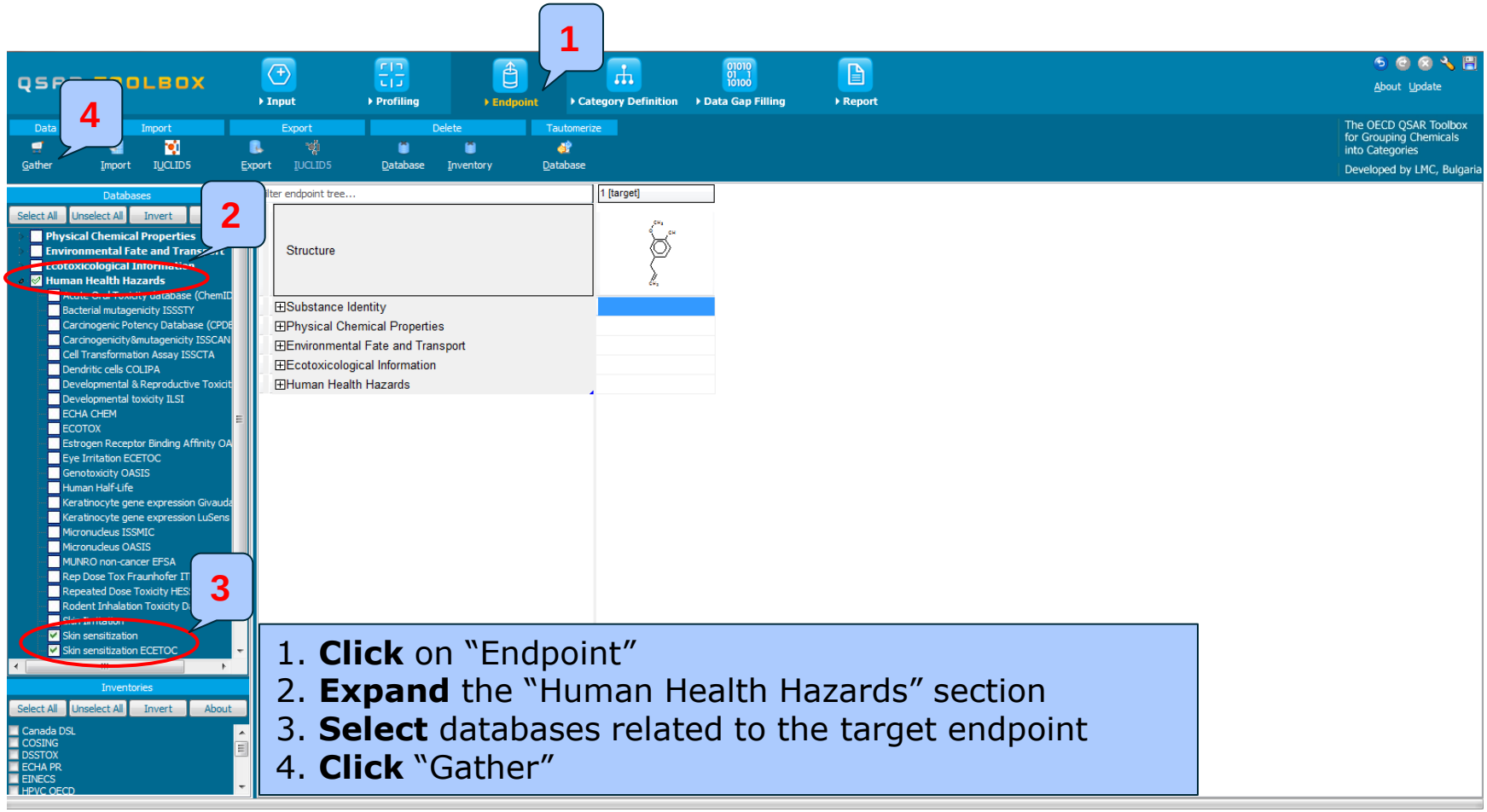
Endpoint
Overview

- "Endpoint" 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).

Endpoint
Case study

- In this example, we limit our data gathering to a single toxicity endpoint (skin sensitization).
- In this example, we collect data from the databases containing experimental results for Skin sensitisation (Skin sensitisation and Skin sensitisation ECETOC).
- Click on "Endpoint" in the Toolbox workflow.
- Expand the "Human Health Hazards" section
- Click on the box to select the relevant databases.
- Click on "Gather data" (see next screen shot).

Endpoint
Gather data



Endpoint
Gather data

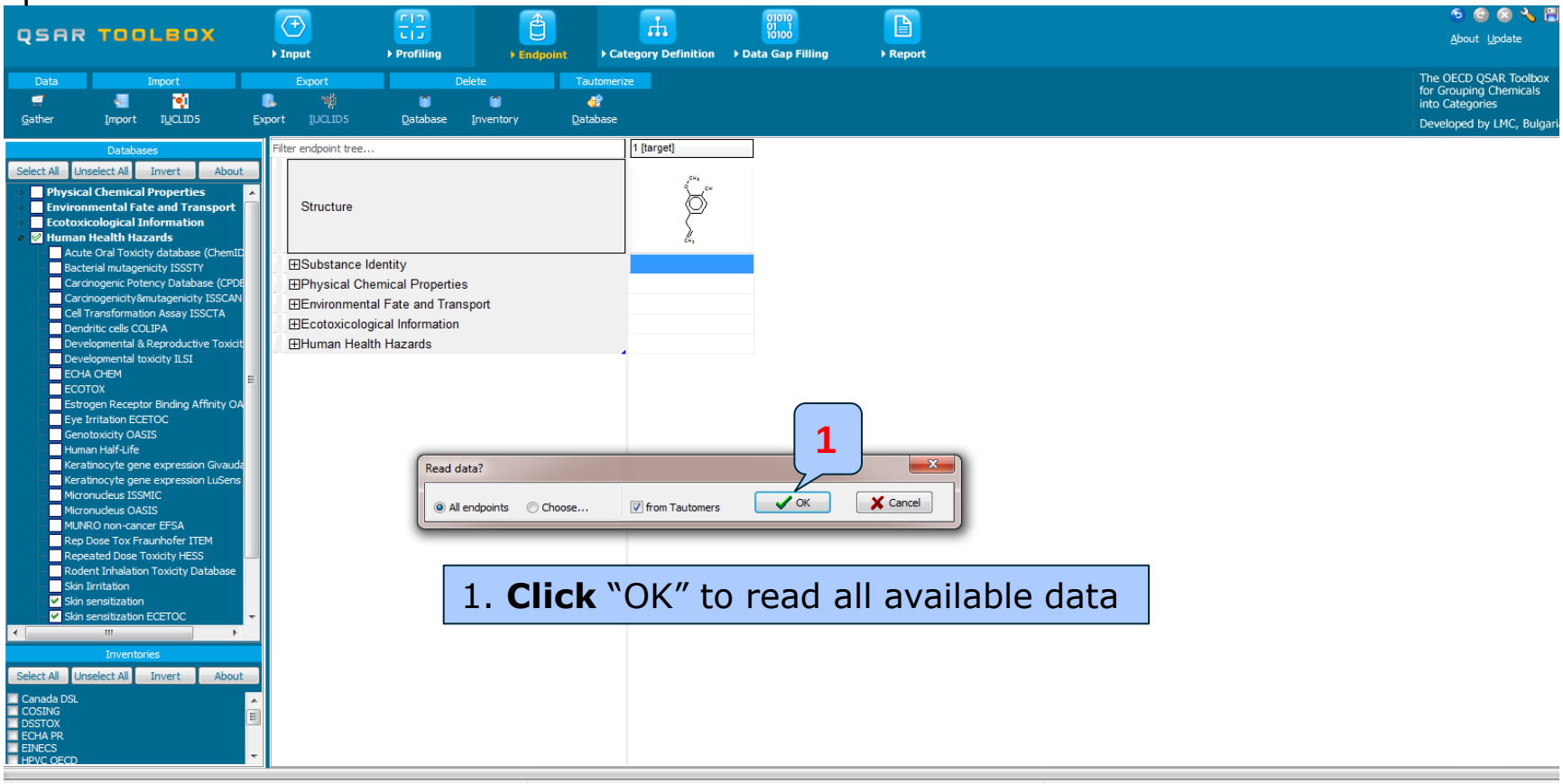
- Toxicity information on the target chemical is electronically collected from the selected dataset(s).

- 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 **Skin sensitization ECETOC .**

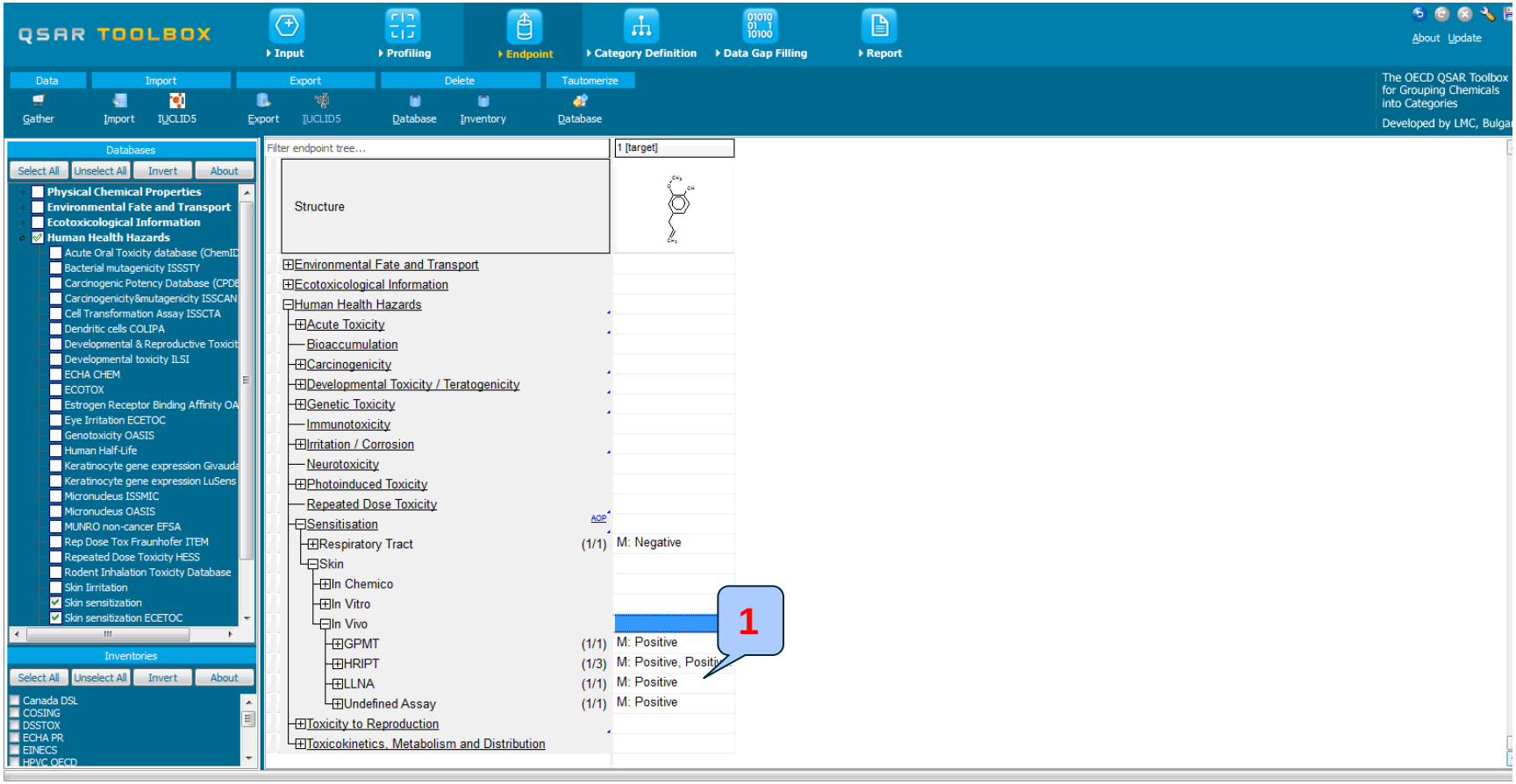
- In this example, there is positive experimental data for the target chemical (see next screen shots).

Endpoint
Gather data

Toxicity information on the target chemical is electronically collected from the selected datasets. A window with "Read data?" appears. Now the user could choose to collect "all" or "endpoint specific" data.

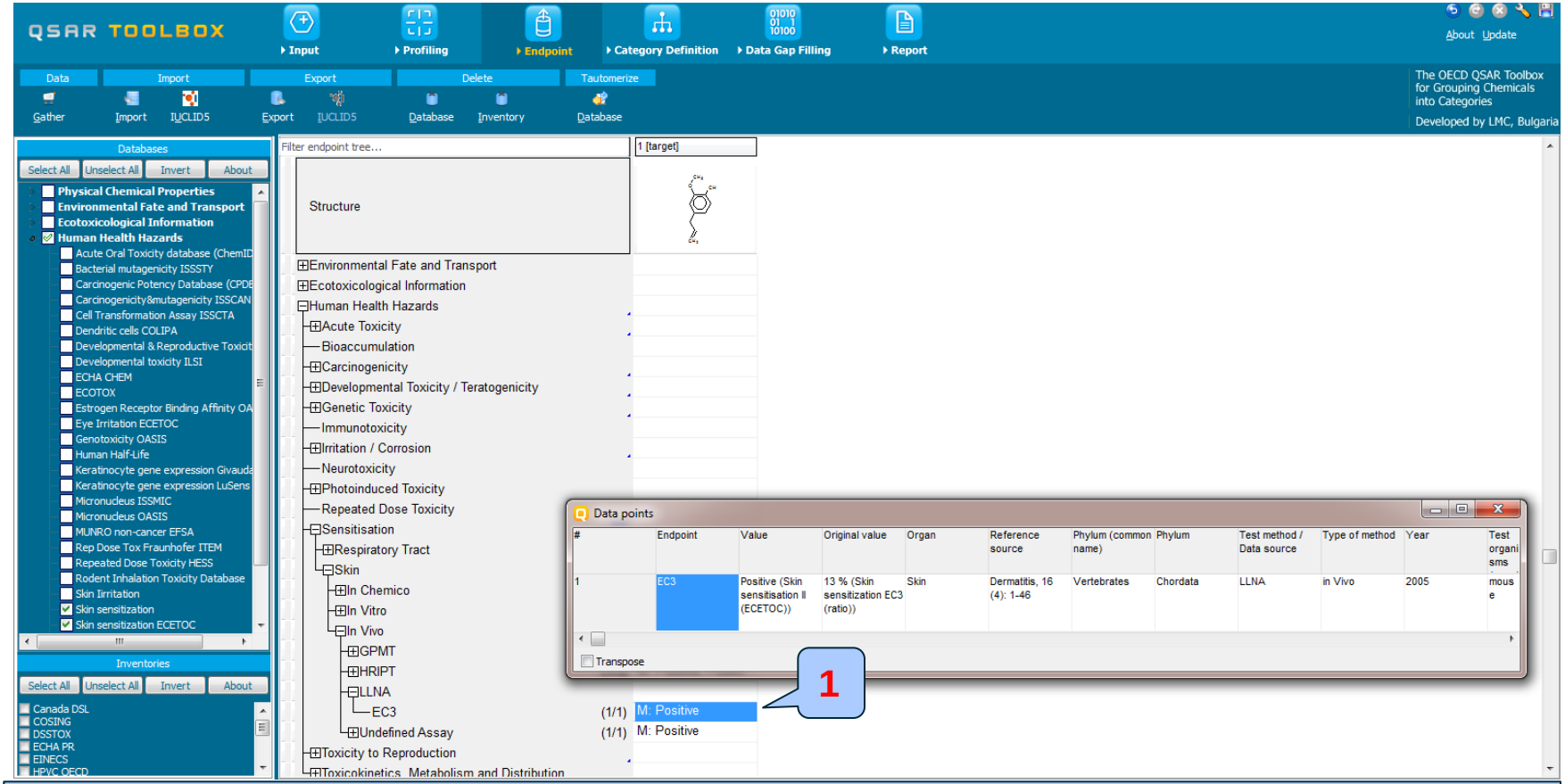


Endpoint
Gather data



1. Positive experimental data for skin sensitization is found for the target chemical.

Endpoint
Gather data



1. **Double-click** on the cell displays metadata information for the observed data

Recap

- The first module, introduces the target chemical, ensure for correctness of the structure.
- The second module shows that there is no protein binding alert for the target chemical.
- In the third module, you have found that the target chemical has positive skin sensitization data.
- In the further read-across analysis we will try to reproduce positive skin sensitization data.
- The study continues with identifying analogues and applying read-across.

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - **Categorization**

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.

- Detailed information about grouping chemical (Chapter 4) could be found in document "Manual for Getting started" published on OECD website:

  http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm

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.

Basic guidance for category formation and assessment

Suitable categorization phases:

1. Structure-related profilers (for primary categorization).
2. Endpoint specific profilers (for sub-cat).
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 suitable categorization phases is shown on next slide

Suitable Categorization/Assessment Phases

Phase I. Structure based

- US EPA Categorization
- OECD Categorization
- Organic functional group
- Structural similarity
- ECOSAR

Broad grouping
Endpoint Non-specific

Repeating Phase I due to Multifunctionality of chemicals

Phase II. Mechanism based

- DNA binding mechanism
- Protein binding mechanism
- Genotoxicity/carcinogenicity
- Cramer rules
- Verhaar rule
- Skin/eye irritation corrosion rules

Subcategorization
Endpoint Specific

Metabolism accounted for

Phase III. Eliminating dissimilar chemicals

Apply Phase I – for structural dissimilarity
Filter by test conditions – for Biological dissimilarity

Subcategorization
Endpoint Specific

Category Definition

Grouping methods – phase I

Suitable Categorization/Assessment Phases

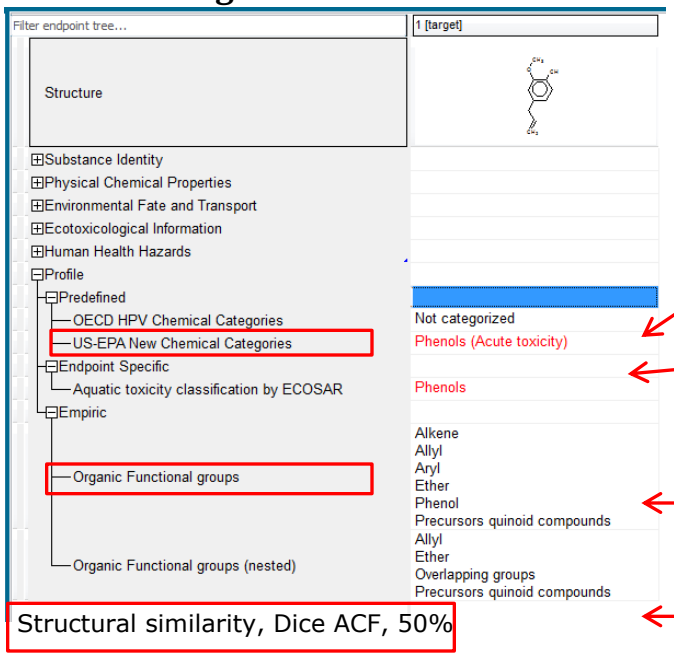
Phase I. Structure based

- US EPA Categorization
- OECD Categorization
- Organic functional group
- Structural similarity
- ECOSAR

Broad grouping
Endpoint Non-specific

Each of the above grouping method is applied to the target chemical and number of the identified analogue is provided below. In order to preserve the basic functional groups available within the molecule: Allyl, Ether and Phenol, OFG is used for categorization purposes. US-EPA and ECOSAR are not used because they omit the other two important functionalities: Allyl and Ether. Str. similarity identifies small set of analogues and apparently could not be used for categorization.

Phase I categorization in Toolbox



128 analogues are identified.

102 analogues are identified

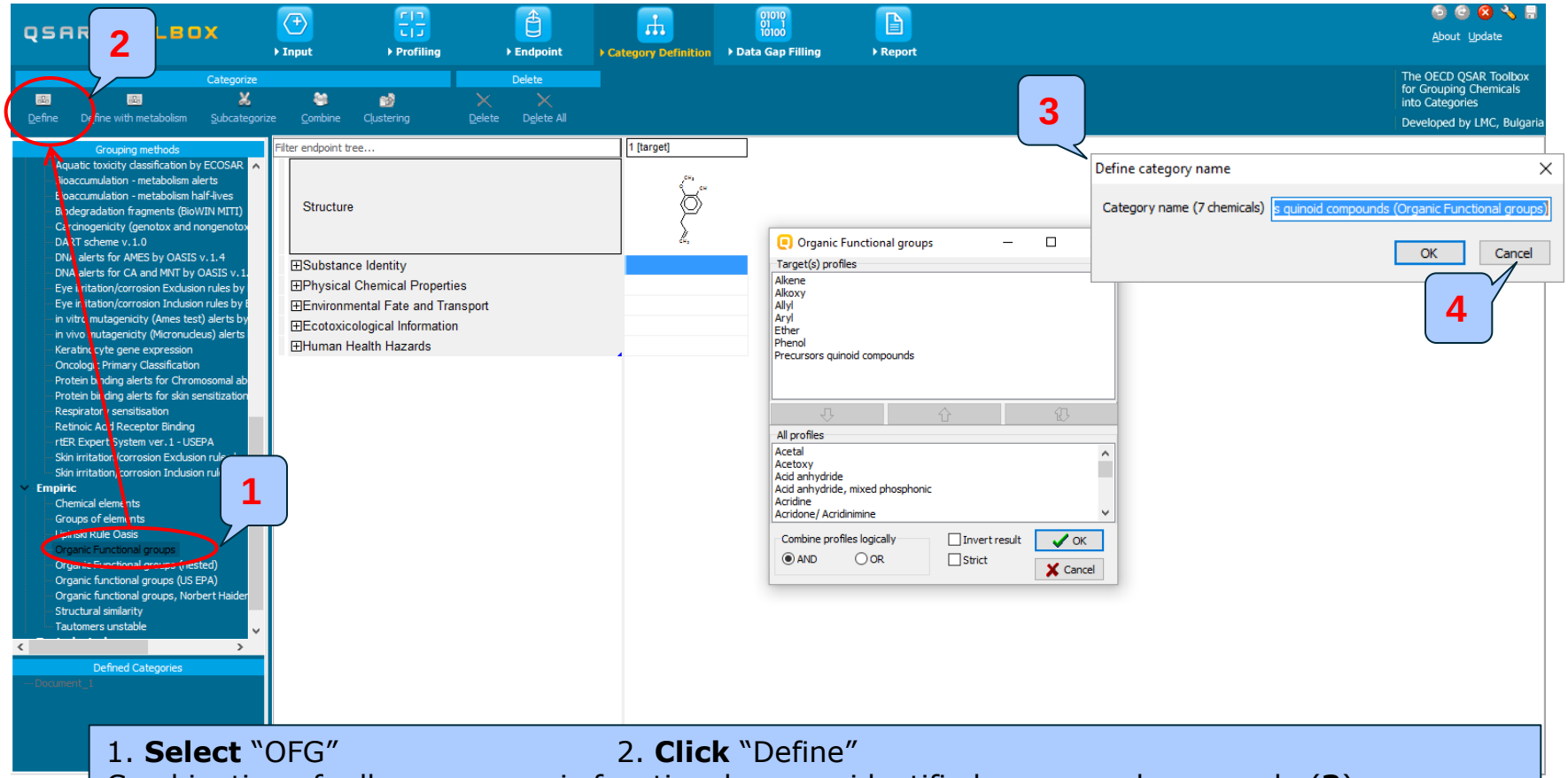
7 analogues are identified (in case all categories are preserved)
11 analogues are identified (in case Allyl, Ether and Phenol are preserved)

Structural similarity, Dice ACF, 50%

21 analogues are identified

Category Definition

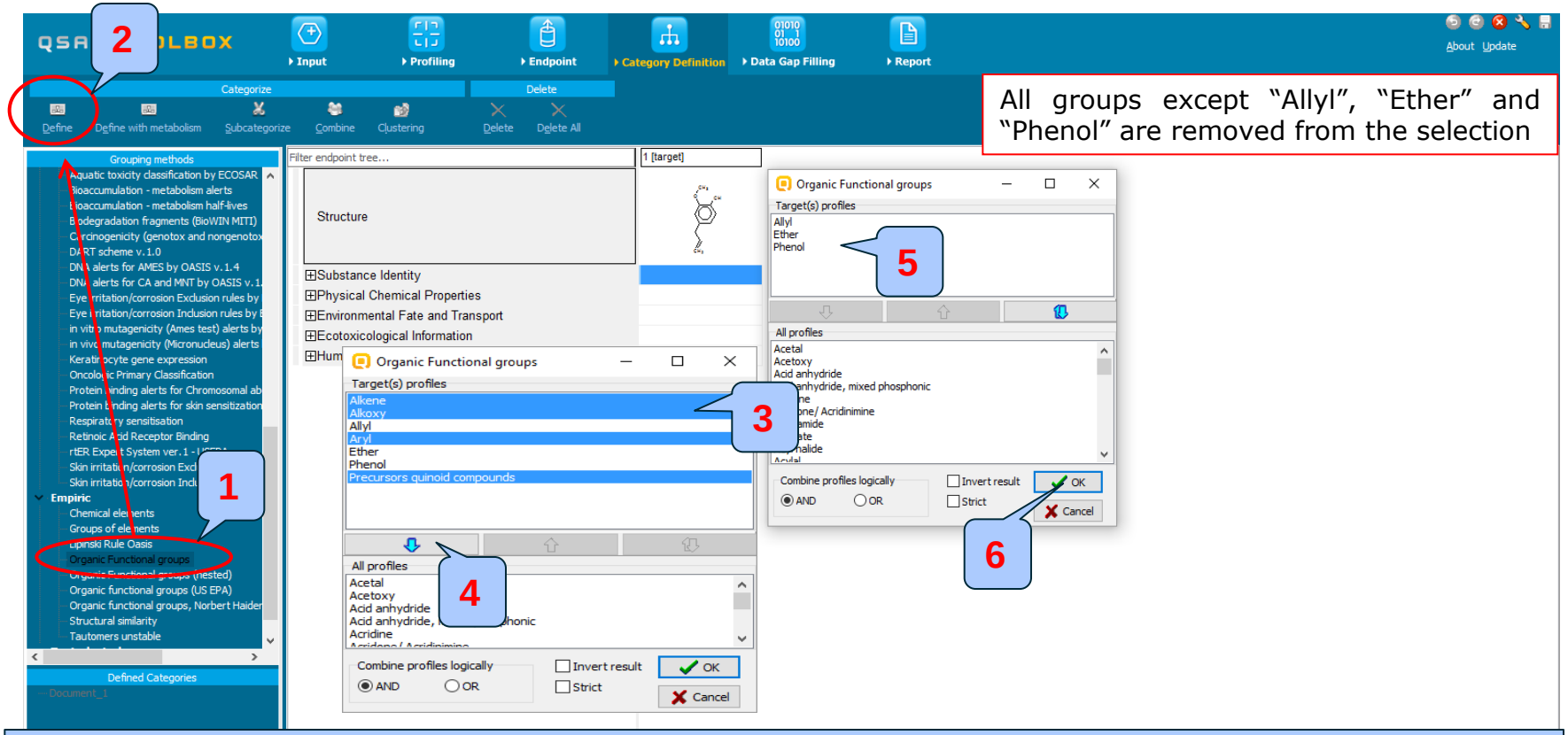
Define category by OFG



1. **Select** "OFG" 2. **Click** "Define"
Combination of all seven organic functional groups identified seven analogues only (**3**).
In order to expand the initial group the categories "Allyl", "Ether" and "Phenol" are used only.
4. **Click** "Cancel". See next slide

Category Definition

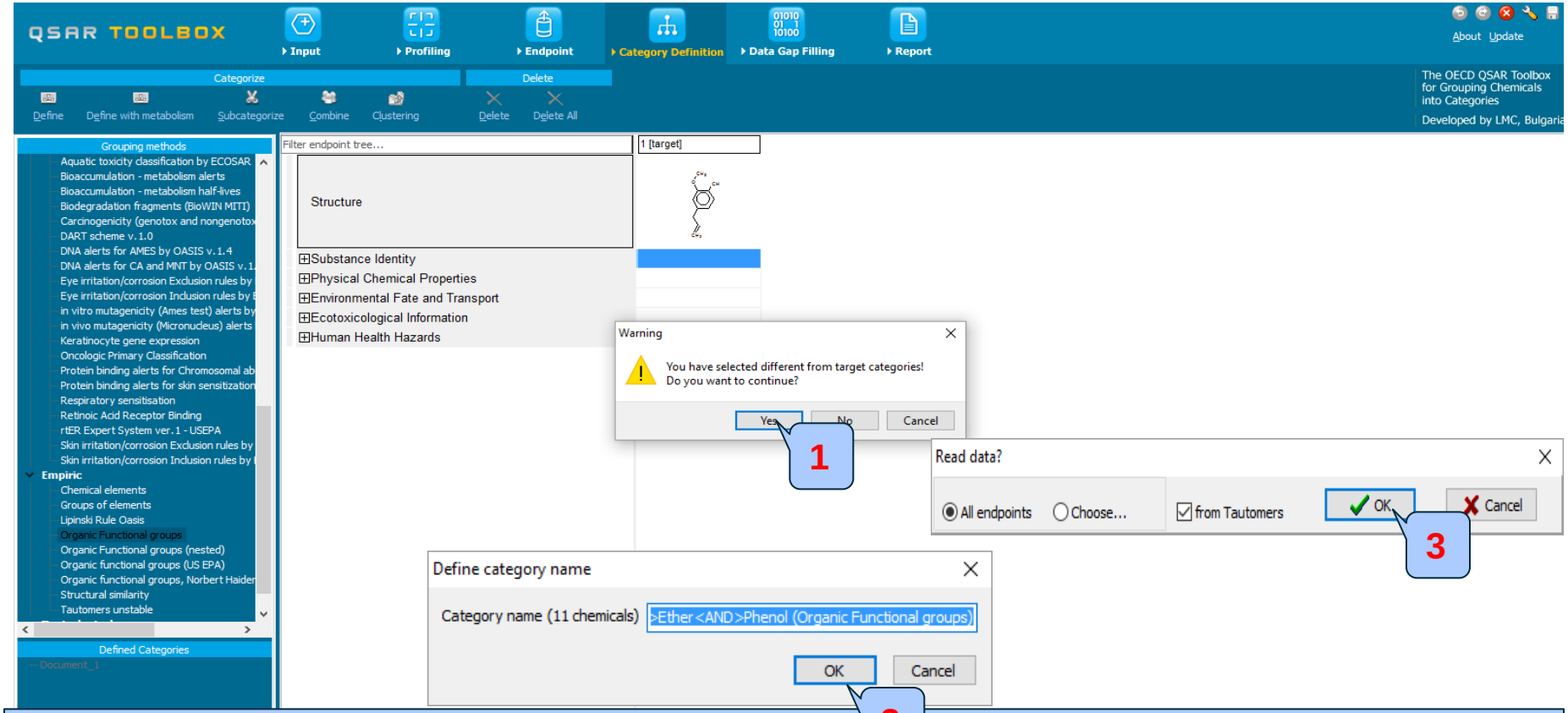
Define category by OFG



1. **Select** "OFG"; 2. **Click** "Define" button; 3. **Select** "Alkenes", "Alkoxy" "Aryl" and "Precursors quinoid compounds" (highlighted in blue) and **click** arrow down to remove them. They are moved in the panel down called "All profiles"; 4. Arrow down
5. "Allyl", "Ether" and "Phenol" should remain in the upper panel only 6.**Click** "OK" button

Category Definition

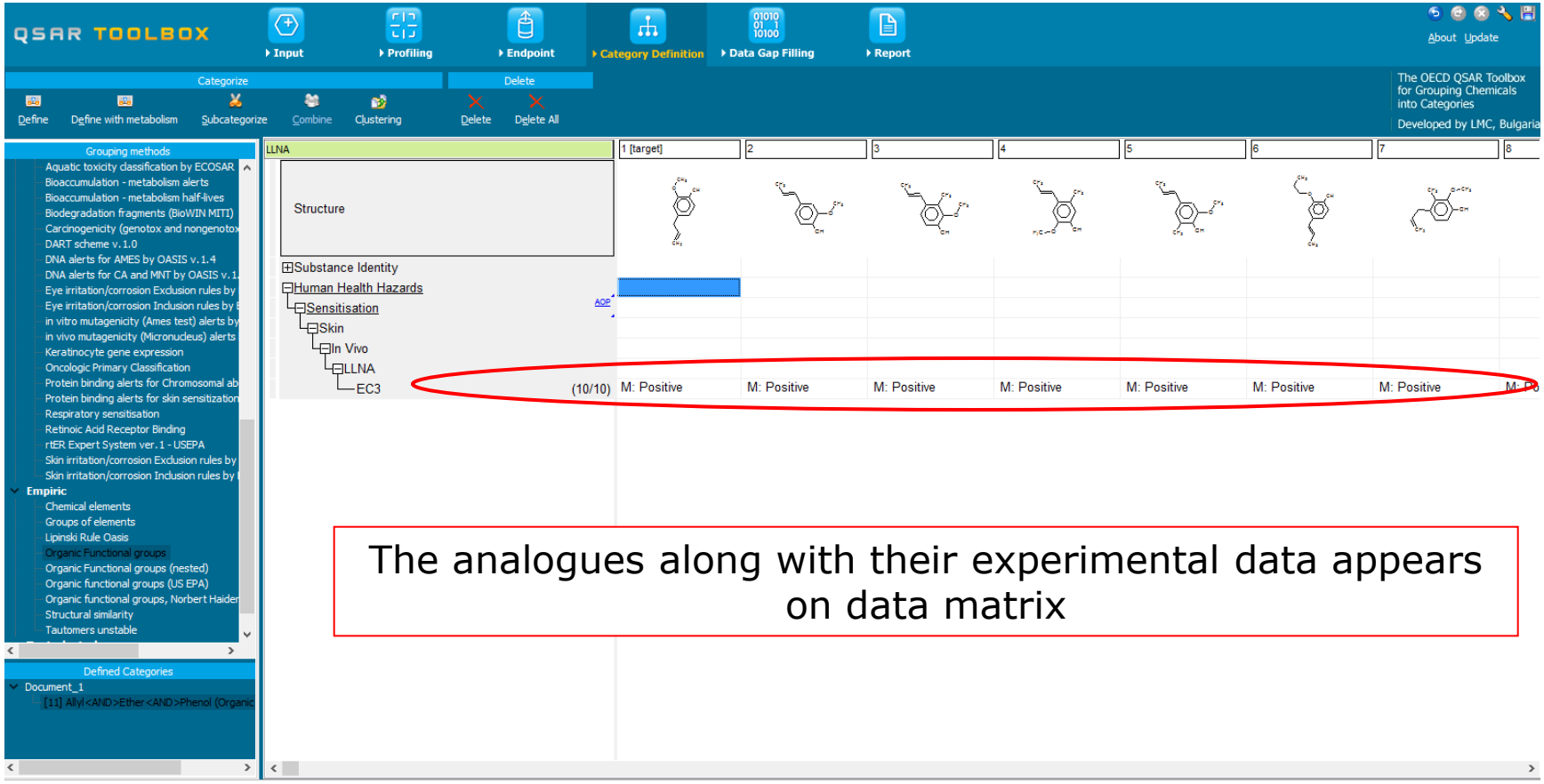
Define category by OFG



1. A message informs for different categories from th of the target have been selected. **Click** "Yes"
2. **Click** "OK" to confirm the name of the category
3. **Click** "OK" to read all available data

Category Definition

Gather data for analogues chemicals



The analogues along with their experimental data appears on data matrix

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - **Data gap filling without taken into account metabolism**

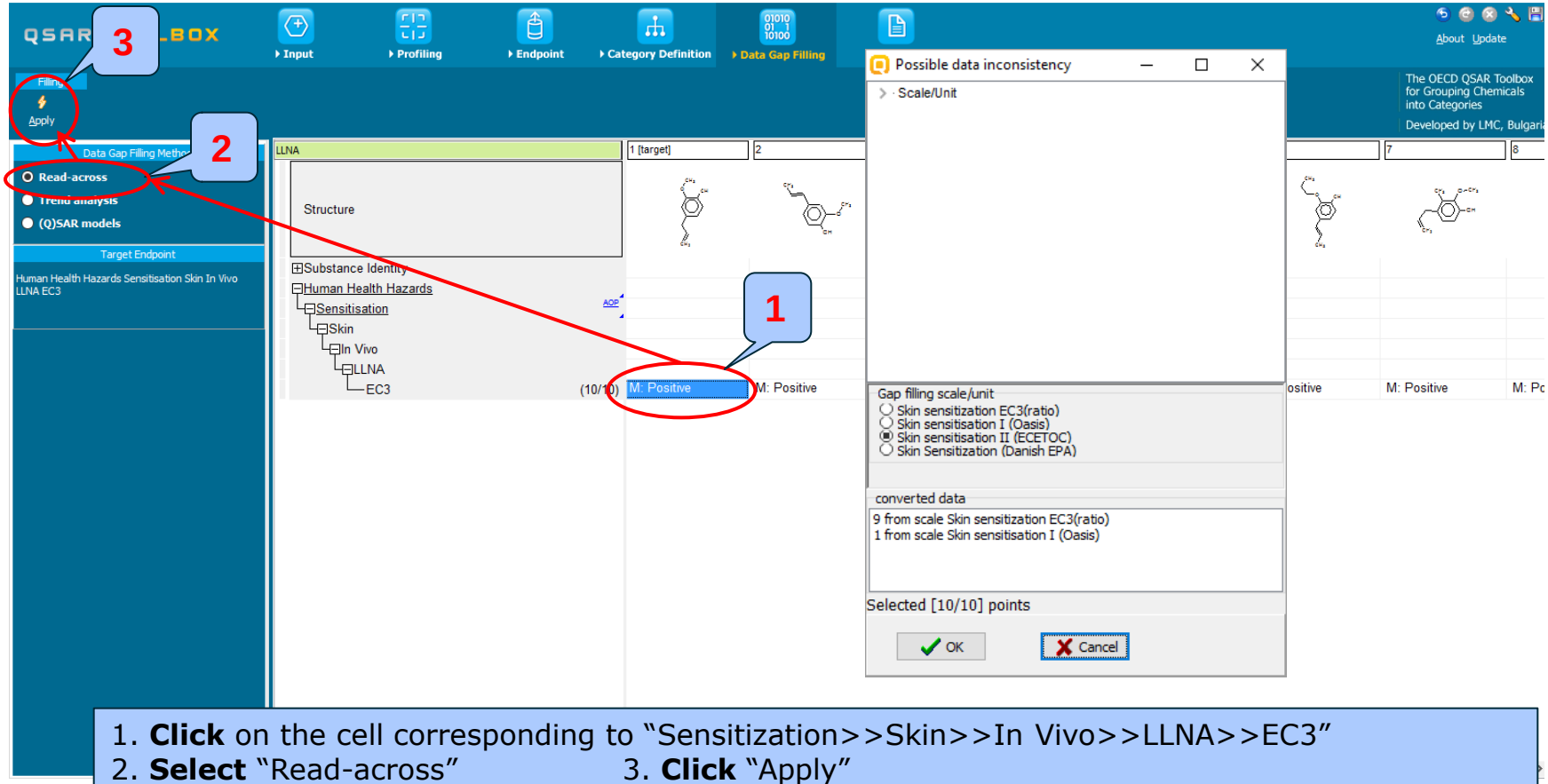
Data Gap Filling
Overview

- "Data Gap Filling" 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.

- In this example, we use read-across.

Data gap filling
Apply Read-across



1. **Click** on the cell corresponding to "Sensitization>>Skin>>In Vivo>>LLNA>>EC3"
2. **Select** "Read-across" 3. **Click** "Apply"

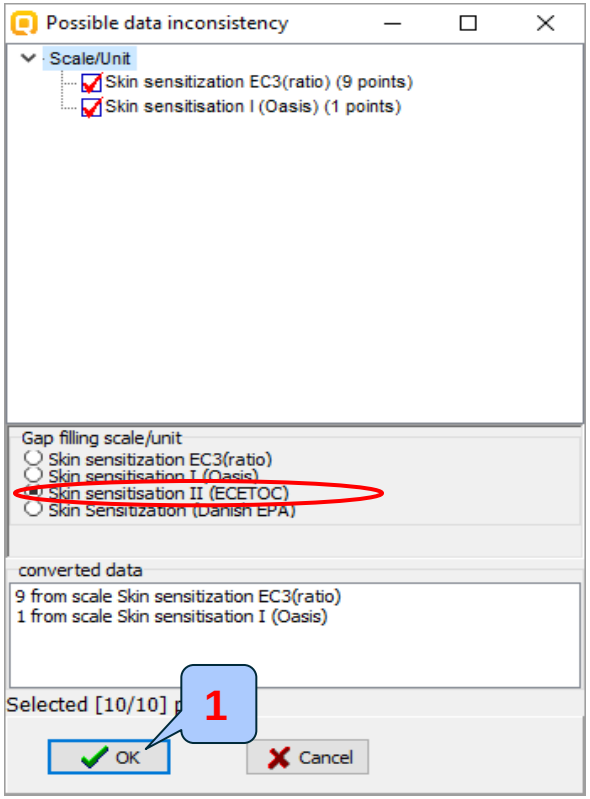
Additional window informing for more than one data/scale has been used appears.
More details about scale definitions is provided on next slide.

Data gap filling
Scale definition

- Skin sensitisation is a "qualitative" endpoint for which the results are presented with categorical data (for example: positive; negative; weak sensitizer; strong sensitizer ,etc).
- Skin sensitisation potential of the chemicals came from different authors coded with different names (for example: data from John Moores University of Liverpool are: *Strongly sensitizing, Moderately sensitizing etc*.; data from European centre for Ecotoxicology and Toxicology of chemicals are: *Positive, Negative, and Equivocal*).
- The main purpose of the scales is to unify all data available in the Toolbox databases for a certain endpoint.
- The default scale for Skin Sensitisation is "Skin Sensitisation ECETOC". It converts all skin data into: Positive, Negative, and Equivocal.

Data gap filling
Scale definition

Back to our example

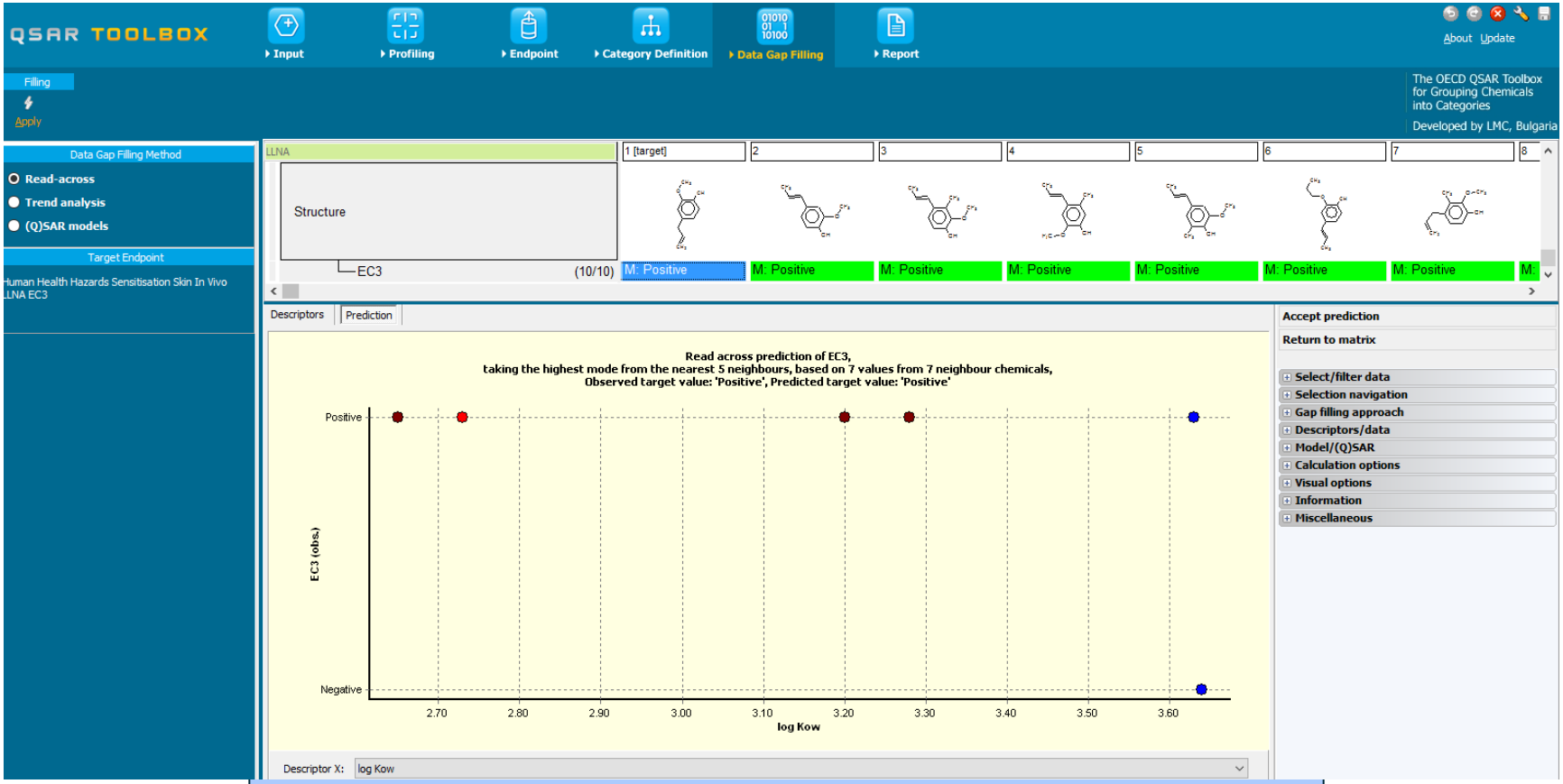


Verify that the default scale "Skin sensitisation II (ECETOC)" is selected
1. **Click** "OK"

Data gap filling
Read-across

- The resulting plot place the experimental results of all analogues (Y axis) according to a descriptor (X axis) which by default is log Kow (see next screen shot).
- The **RED** dot represents predicted results for the target chemical.
- The **BROWN** dots represent the experimental results available for the analogues that are used for the read-across.
- The **BLUE** dot represent the experimental results available for the analogues but not used for read-across.

Data gap filling
Read-across



Initial graph without any subcategorizations

Data Gap Filling
Subcategorizations

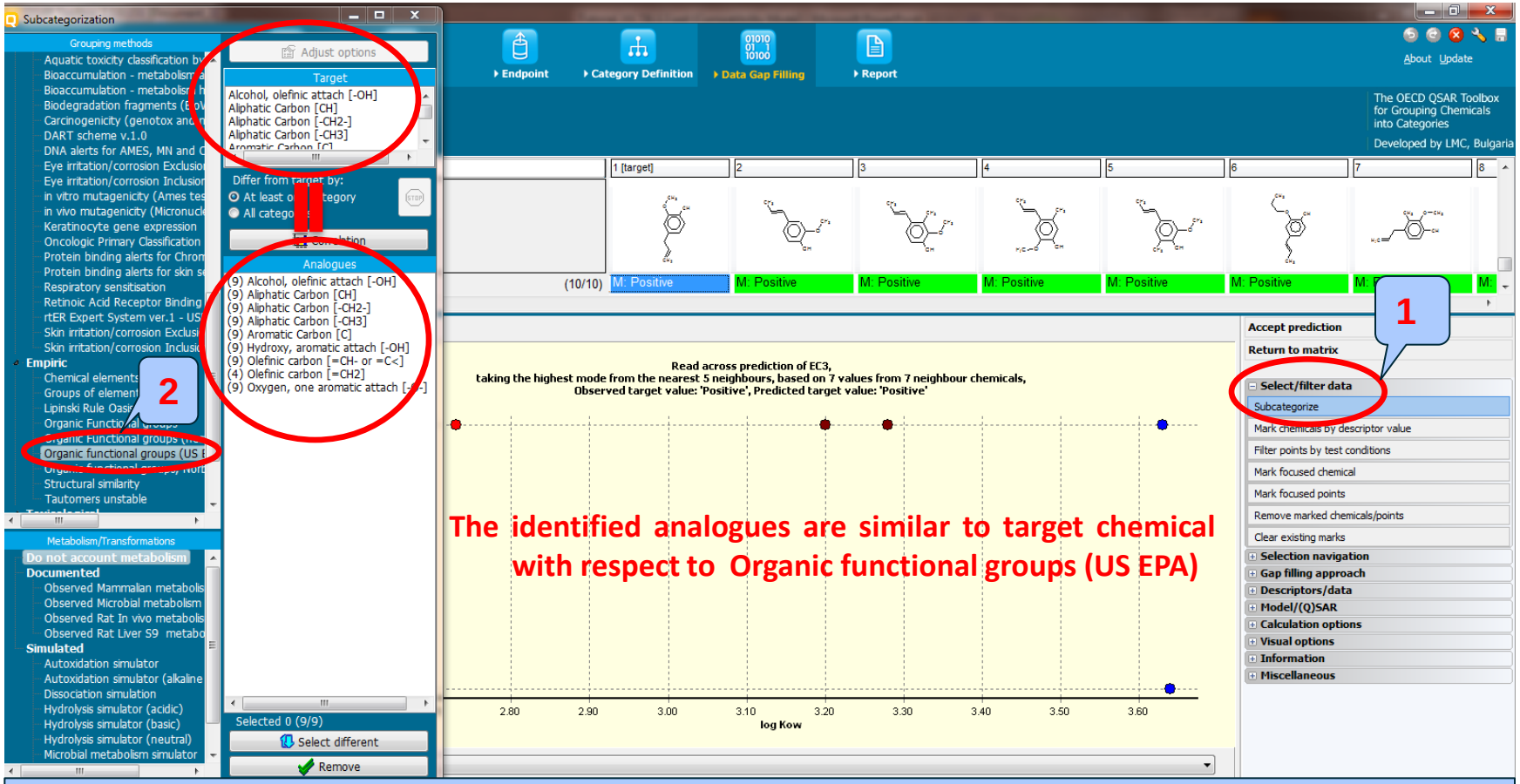
In this example, the following subcategorizations are applied in order to eliminate dissimilar analogues (see slide 44):

- Organic functional group (US-EPA) – phase I is repeated in order to eliminate multifunctional analogues (subcategorization 1)
- Protein binding alerts for skin sensitization by OASIS v1.4 (subcategorization 2)

See next screen shots.

Data gap filling

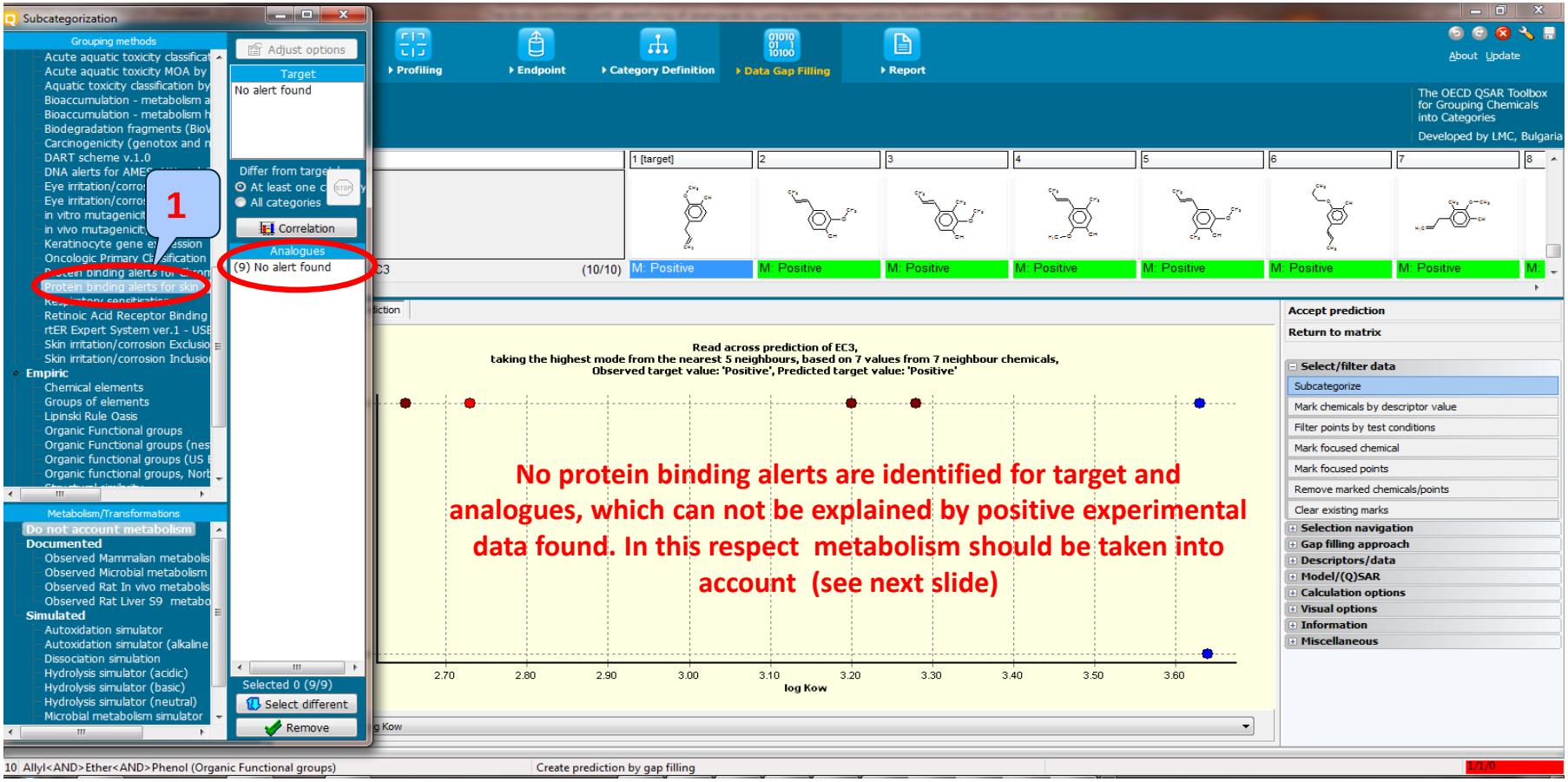
Subcategorization 1: Organic functional groups (US EPA)



1. **Open** "Select/filter data/Subcategorize" 2. **Select** "Organic functional groups (US EPA)"

Data gap filling

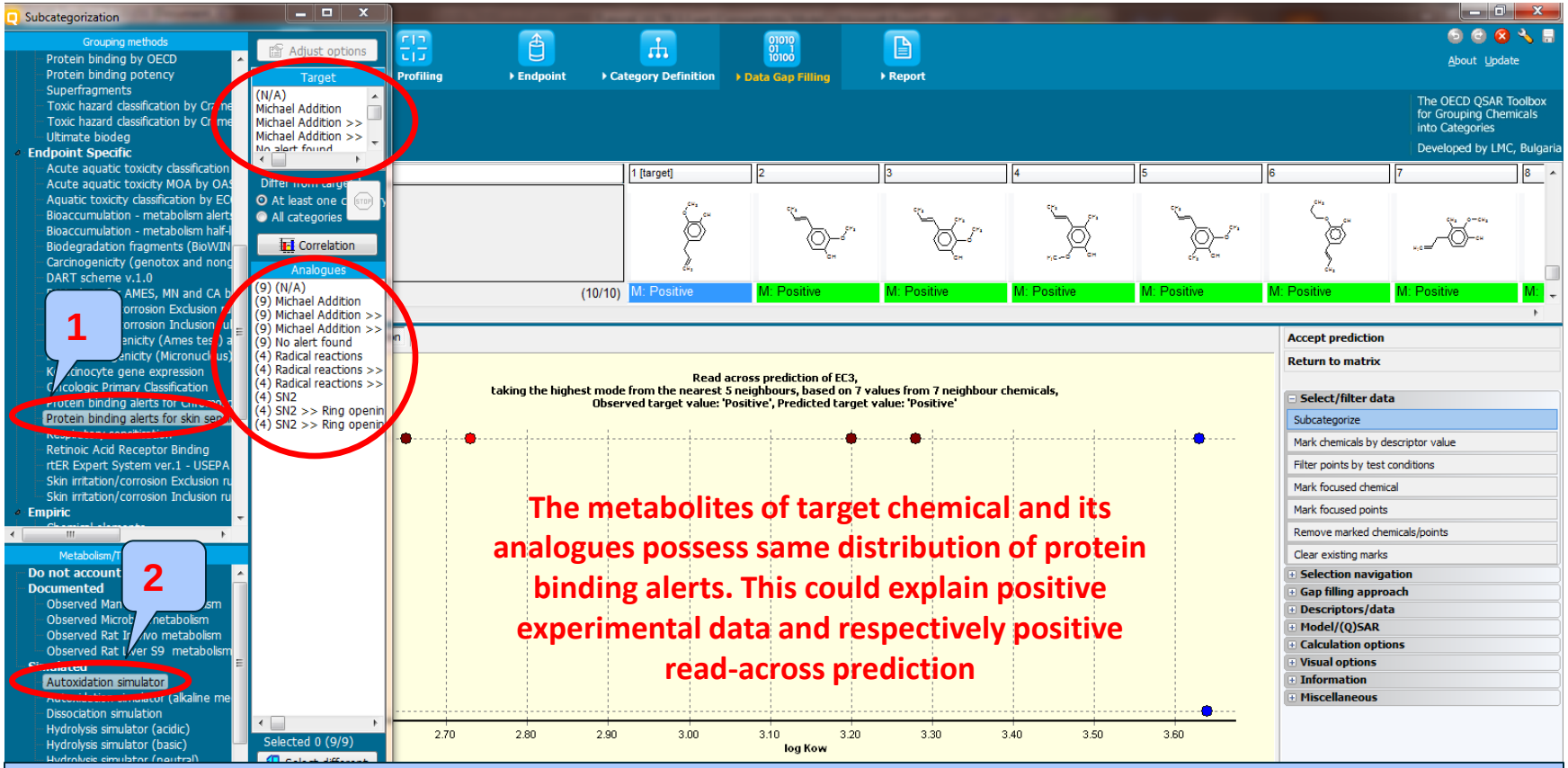
Subcategorization 2: Protein binding alerts for skin sensitization by OASIS v.1.4



1.**Select** "Protein binding alerts for skin sensitization by OASIS v1.4"

Data gap filling

Subcategorization when metabolism is taken into account



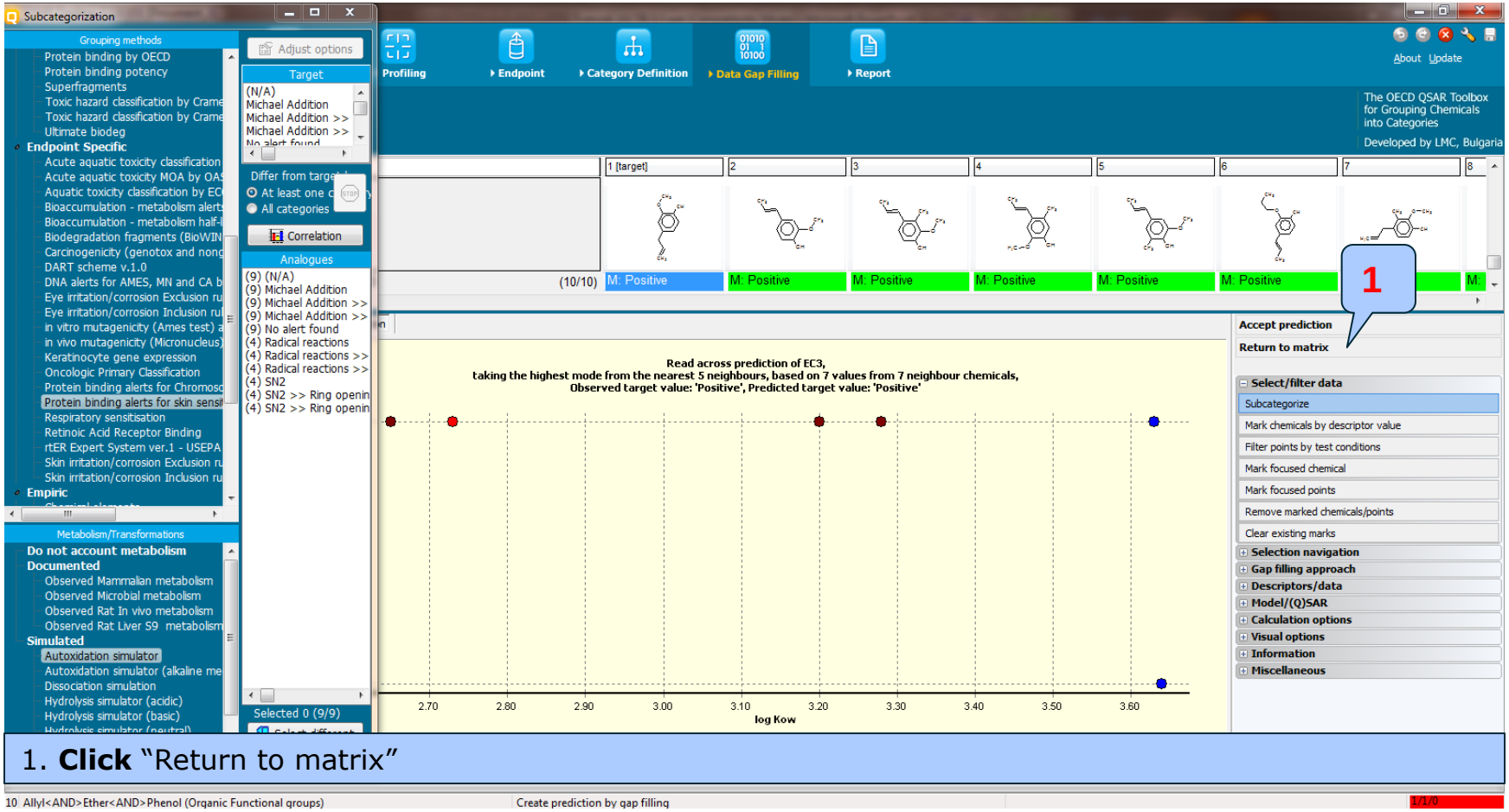
Now subcategorization will be applied accounting for autoxidation simulation in combination with "Protein binding alerts" on the target and its analogues. Follow the steps:

1. The "Protein binding alerts for skin sensitization by OASIS v1.4" has been already selected;
2. **Click over** "Autoxidation simulator"

Data gap filling
Interpreting Read-across

- In this example the target and all analogues have no protein binding alerts.
- All analogues along with the target possess same distribution of positive protein binding alerts when autoxidation is taken into account.
- The latter could explain the positive experimental data of the target compound.
- Once ready go back to data matrix, when click on “Return to matrix” button (see next slide).

Data gap filling
Return to data matrix



1. **Click** "Return to matrix"

Data gap filling
Next actions

- The study continues with second data gap filling where a category of analogues is defined by using new categorization functionality allowing to define category accounting for (a)biotic activation of the target.

- Before proceeding with Data gap filling the following two items will be illustrated intended to explain and support the analysis. Following the steps is not necessary.

  - Multiplication of the target chemical

  - Profiling the parent and metabolites based on (a)biotic activation

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - **Multiplication of the target chemical**

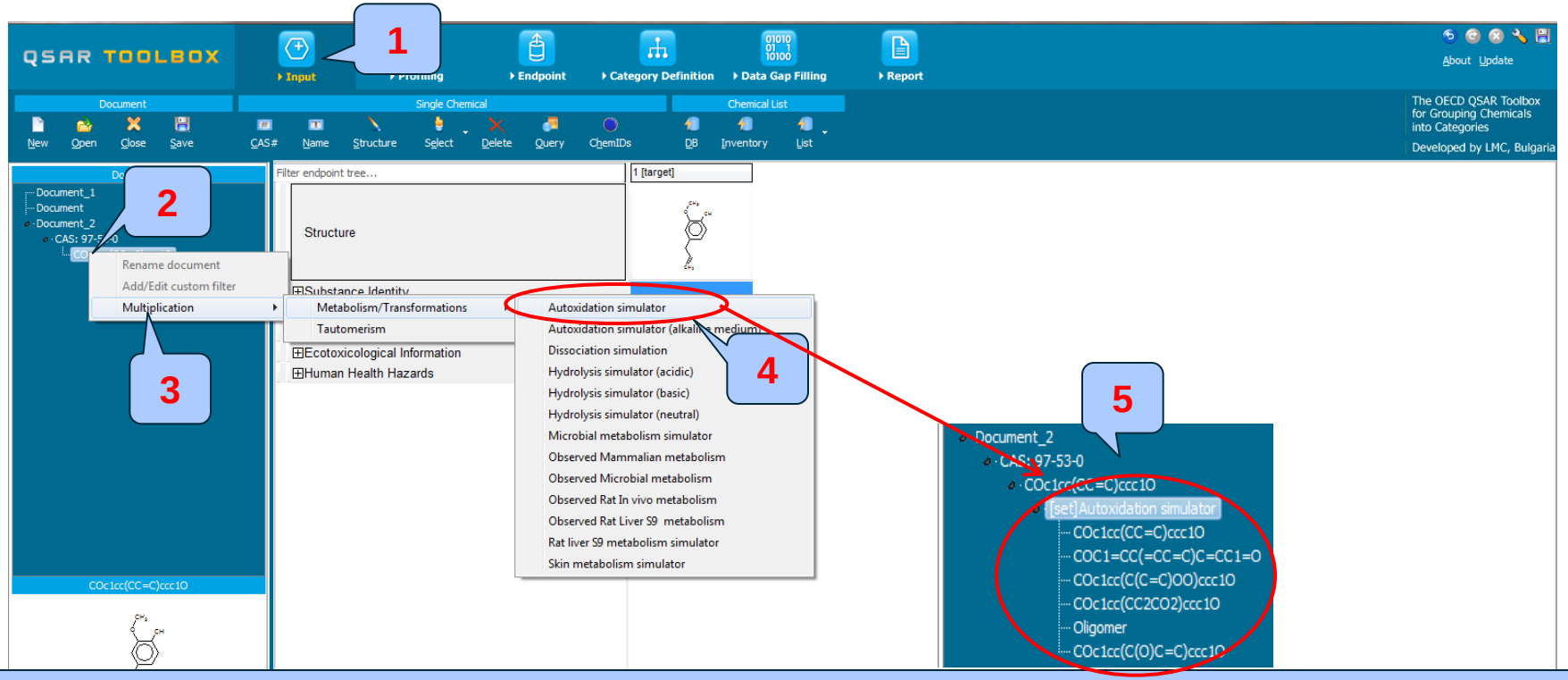
Multiplication of the target chemical

- Multiplication of the target chemical could be accomplished by two ways:
  - In the **Input** section outside data gap filling module (scenario 1) – slide 66
  - In the **Profiling** section (scenario 2) – slide 69
- Both scenarios will be demonstrated on next few slides

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - **Multiplication of the target chemical**
    - **In the Input section (scenario 1)**

Multiplication of target chemical in the Input section (scenario 1)



1. **Go to "Input"**
2. **Click** over the SMILES of the target chemical and perform **right click** on it, then
3. **Select** "Multiplication-Metabolism/Transformations"
4. **Select** "Autoxidation simulator"
5. Generated metabolites appeared in a tree-like form. They could be visualized in two modes. See next slide

Multiplication of target chemical in the Input section (scenario 1)

Visualization the set of parent and metabolites

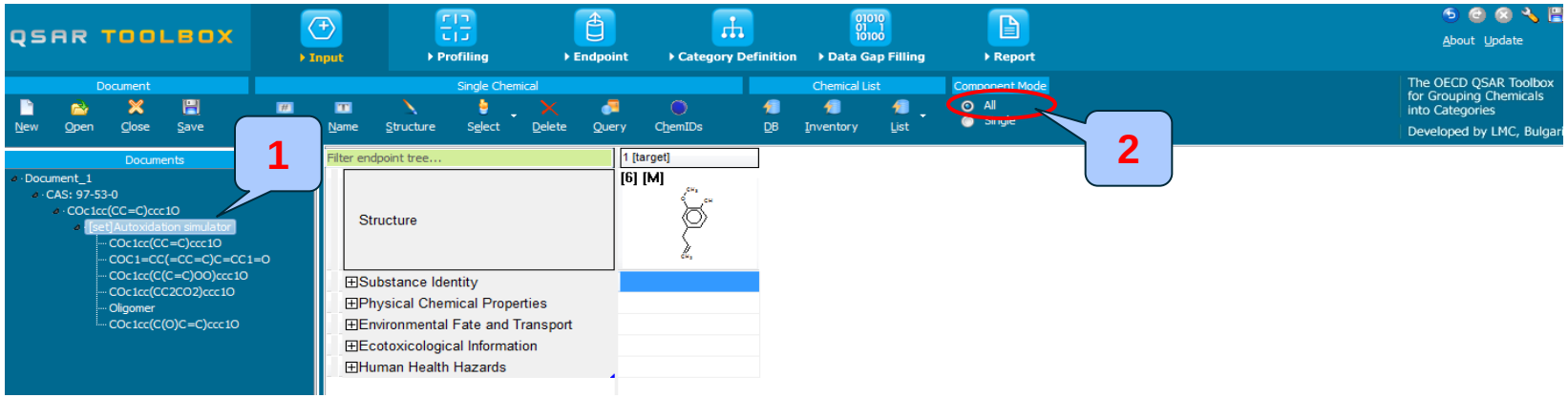
- Two component modes are implemented:
  - Set Mode - all metabolites are analysed as a package
  - Individual Component Mode - each metabolite is analysed individually

(graphical illustration of both modes is provided next screenshot)

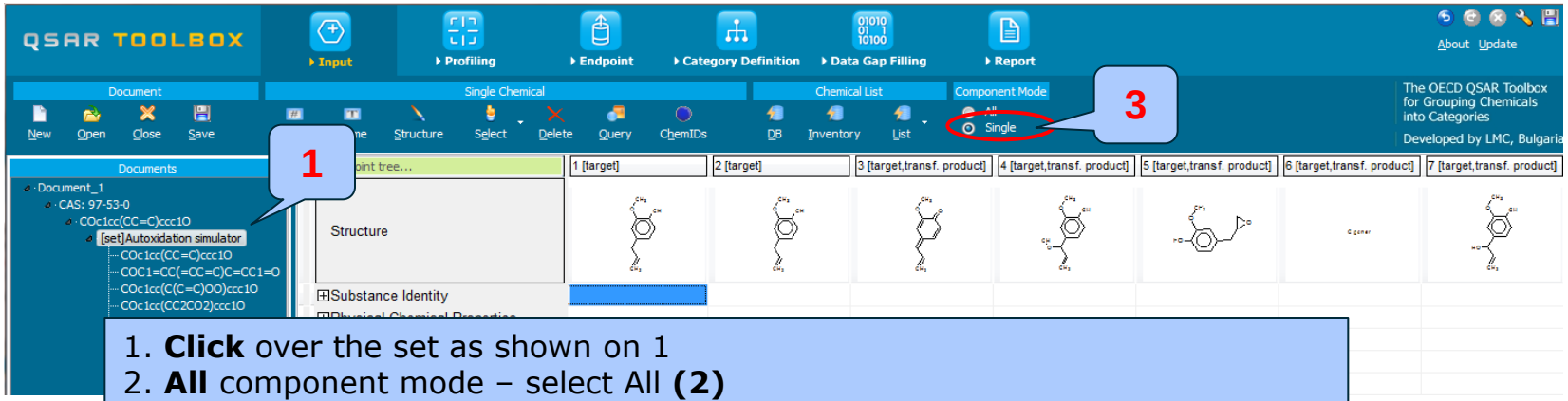
Multiplication of target chemical in the Input section (scenario 1)

Visualization the set of parent and metabolites

- All Component Mode – all metabolites are analyzed as a package



- Single Mode – each metabolite is analyzed individually

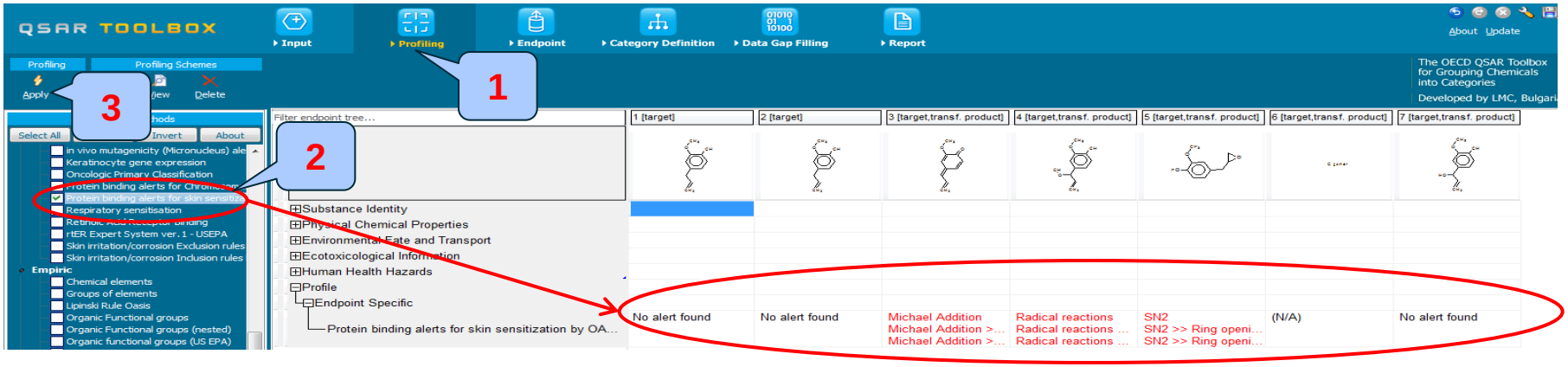


1. **Click** over the set as shown on 1
2. **All** component mode – select All **(2)**
3. **Single** component mode – select Single **(3)**

Protein binding result for parent and metabolites multiplied in the Input section

Autoxidation simulator

The profiling result indicates no protein binding alerts for target chemical. However, three of simulated AO metabolites exhibit interaction with proteins via three different protein binding mechanisms (Michael Addition, Radical reactions, and SN2).

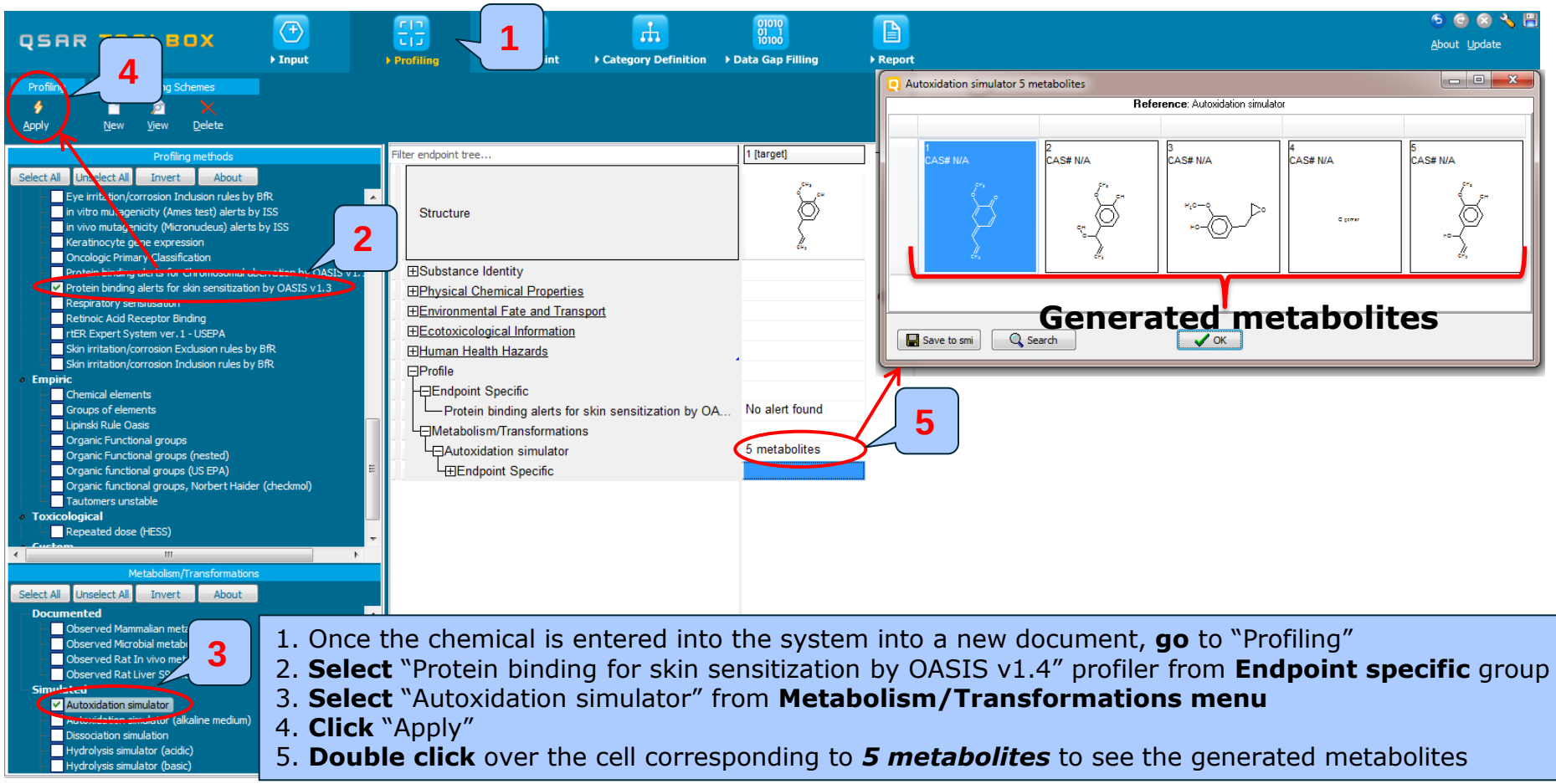


Once the chemical is multiplied in the Input section and metabolites are visualized (distributed on data matrix) via "Single mode" 1. **Go** to "Profiling"; 2. **Check** "Protein binding alerts for skin sensitization by OASIS v1.4"; 3. **Click** "Apply"

Outlook

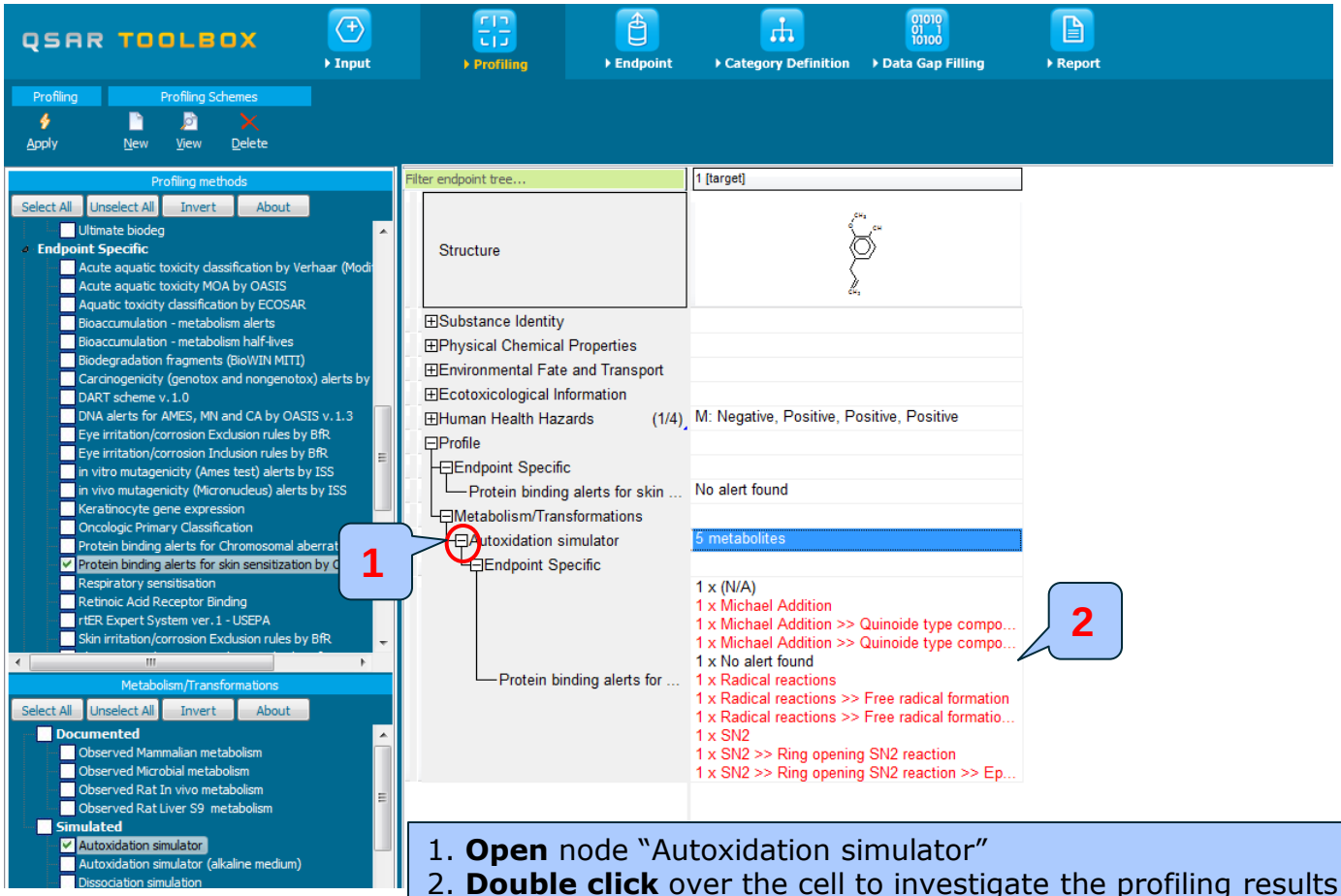
- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - **Multiplication of the target chemical**
    - In the Input section (scenario 1)
    - **In the Profiling section (scenario 2)**

Multiplication of target chemical in the Profiling section (scenario 2)



1. Once the chemical is entered into the system into a new document, **go** to "Profiling"
2. **Select** "Protein binding for skin sensitization by OASIS v1.4" profiler from **Endpoint specific** group
3. **Select** "Autoxidation simulator" from **Metabolism/Transformations menu**
4. **Click** "Apply"
5. **Double click** over the cell corresponding to ***5 metabolites*** to see the generated metabolites

Protein binding result for parent and metabolites multiplied in the Profiling section

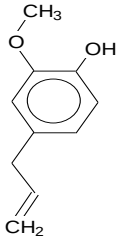


1. **Open** node "Autoxidation simulator"
2. **Double click** over the cell to investigate the profiling results obtained for the metabolites

Recap

Parent

Eugenol
CAS# 97-53-0



Protein binding alert
(Protein binding by OASIS)

No alert found

Experimental data

LLNA
Strong sensitizer

Data gap filling

No protein binding alerts

Positive RA prediction

How to explain positive RA ?

Autoxidation Simulator/Skin metabolism

Protein binding alert found for package of metabolites

next

Categorization with metabolism

Identifying protein binding analogues of the target taking into account its metabolic activation

Outlook

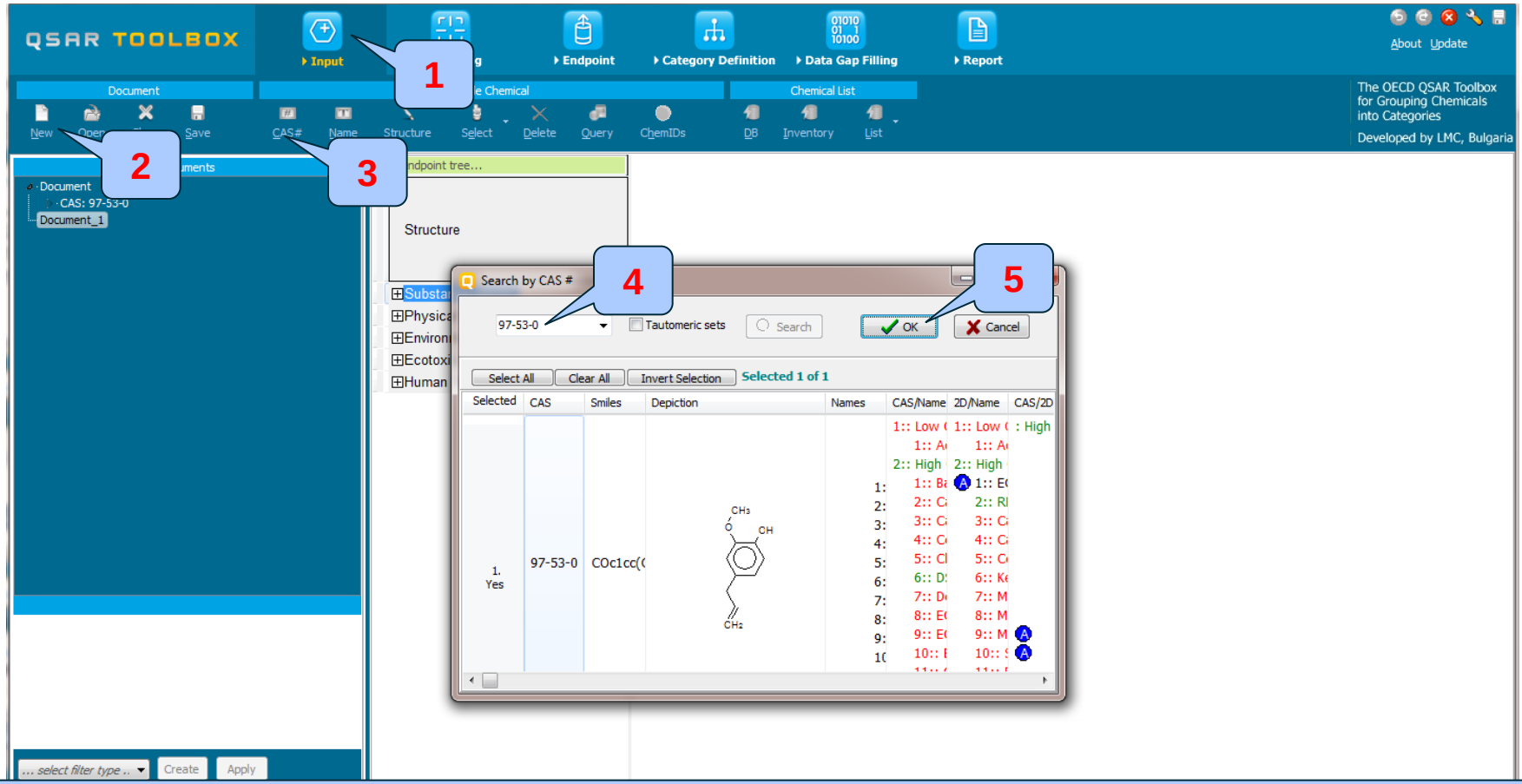
- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - Multiplication of the target chemical
  - **Categorization applying metabolism**

Categorization applying metabolism

The advantages of the new functionality are:

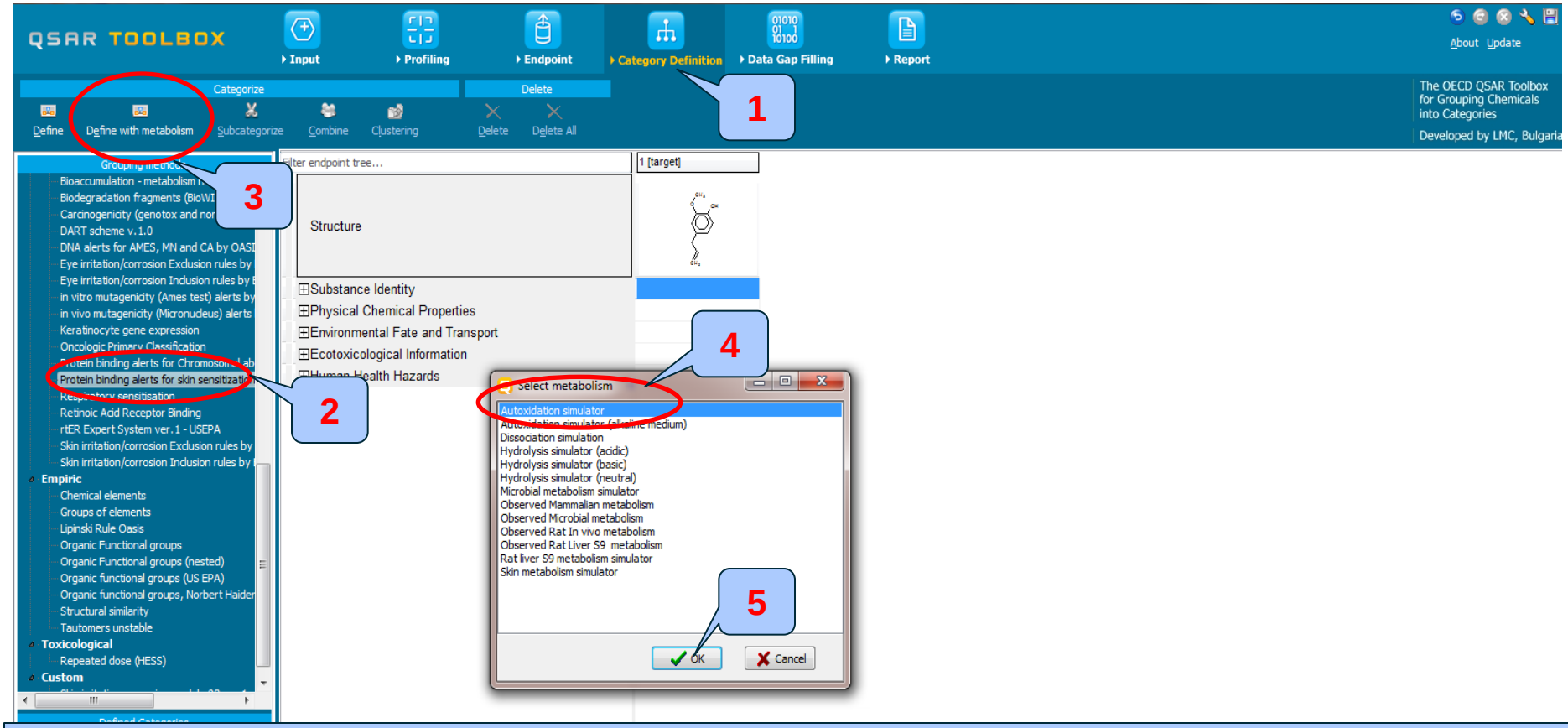
- Application of metabolism for analogues identification during process of categorization. Metabolism could be used for primary categorization.
- Possibility to expand the chemical domain of the category and to identify analogues based on metabolism approach.
- Before proceeding with categorization accounting for (a)biotic activation of the target input the target in a new document (see next slide).

Categorization applying metabolism



1. **Go** to "Input" section; 2. **Click** on "New" button; 3. **Click on** "CAS#" button; 4. **Enter** the CAS number of the target
5. **Click** "OK"

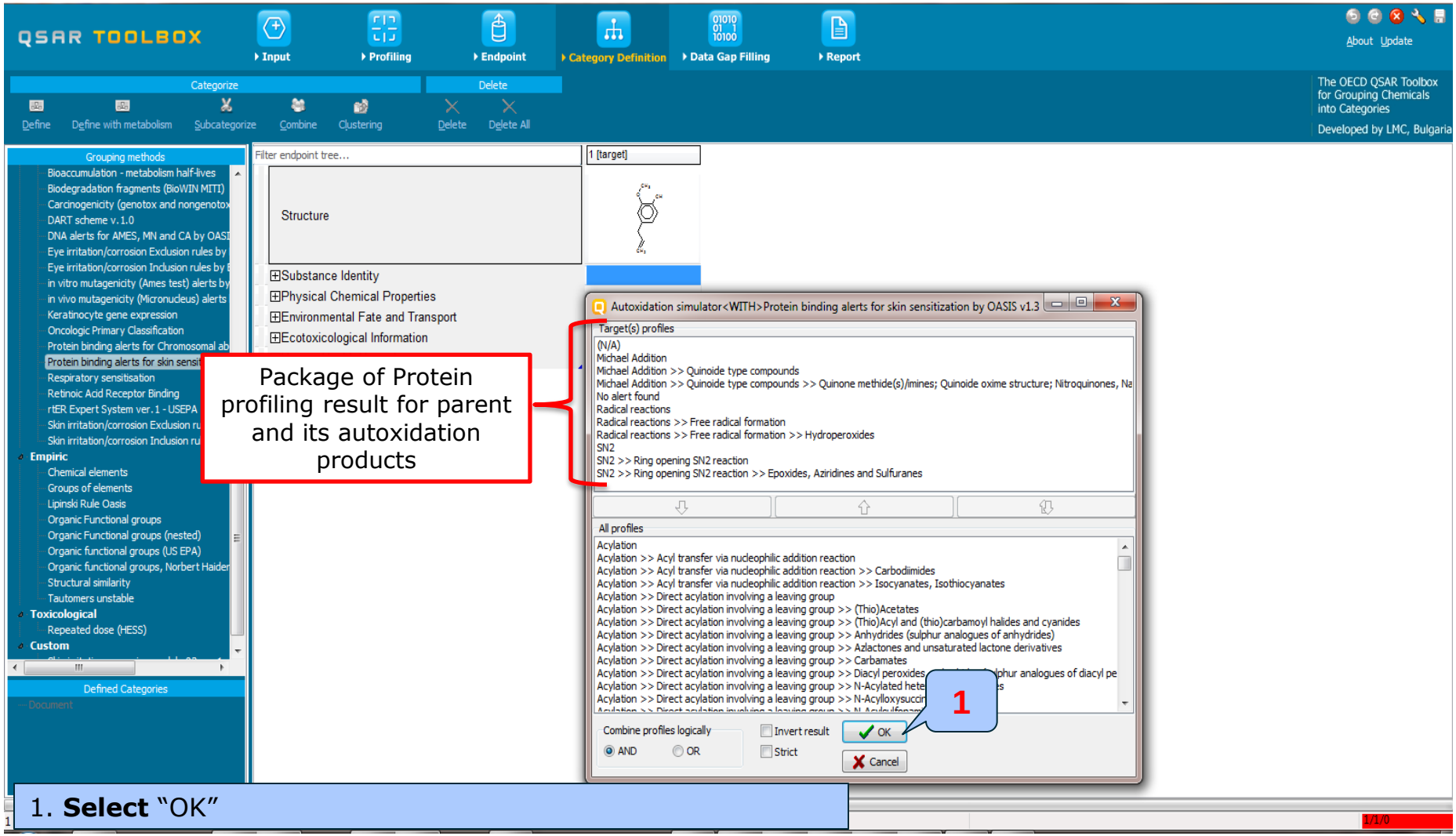
Categorization applying metabolism



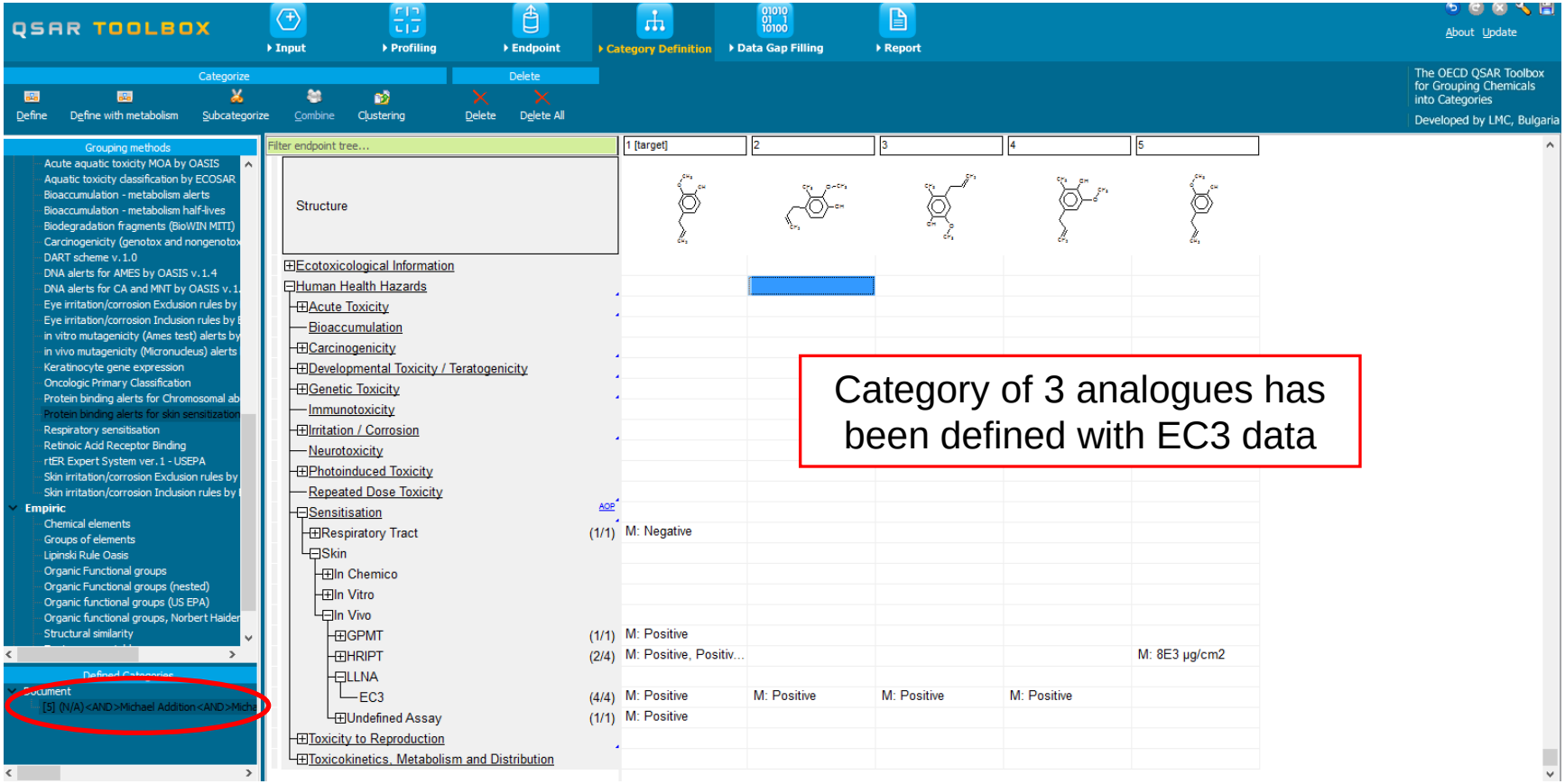
1. **Go** to "Category Definition" section; 2. **Click on** "Protein binding alerts for skin sensitization by OASIS v1.4"; 3. **Click on** "Define with metabolism" button; 4. **Select** "Autoxidation simulator" 5. **Click** "OK" (additional window appears, see next slide)

Note: In some cases this process may take longer time, due to not indexed results for the rest of the simulators.

Categorization applying metabolism



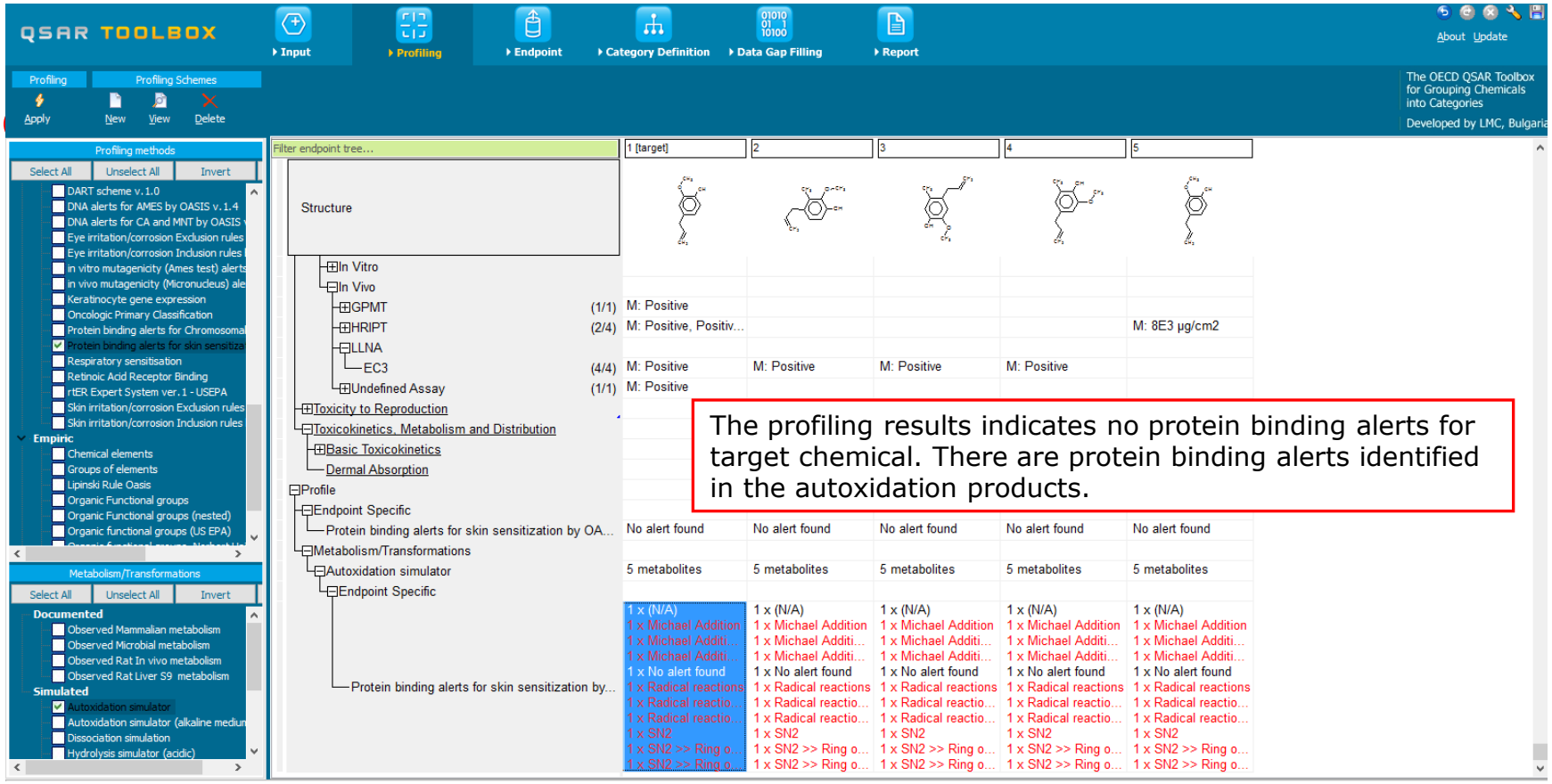
Categorization applying metabolism



The forthcoming two slides illustrates how consistent is the identified category with respect to protein binding alerts when metabolism is taken into account

Categorization applying metabolism

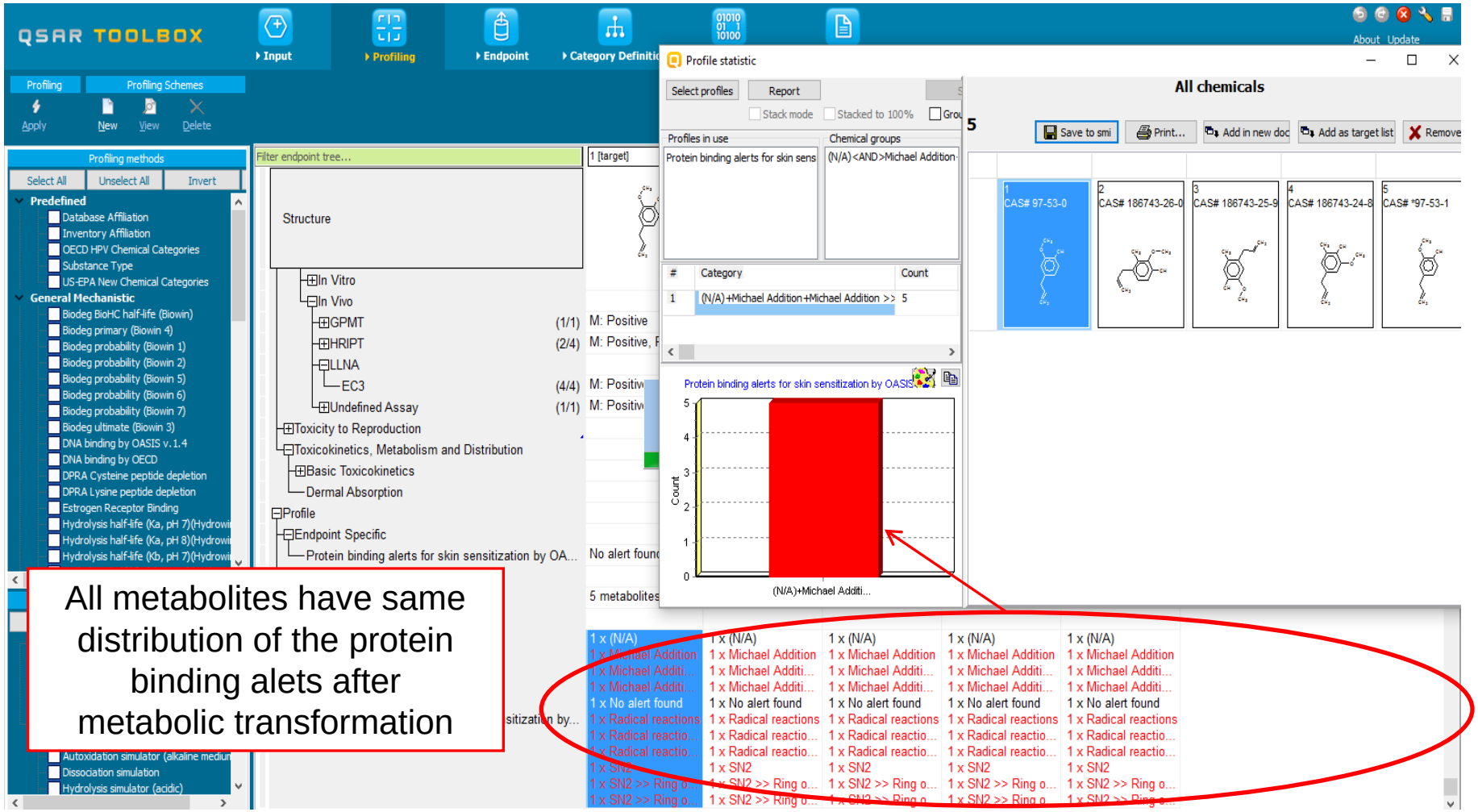
Profiling results for parent and metabolites



1. **Go** to "Profiling"; 2. **Check** "Protein binding alerts for skin sensitization by OASIS v1.4"
3. **Check** "Autoxidation simulator"; 4.**Click** "Apply"

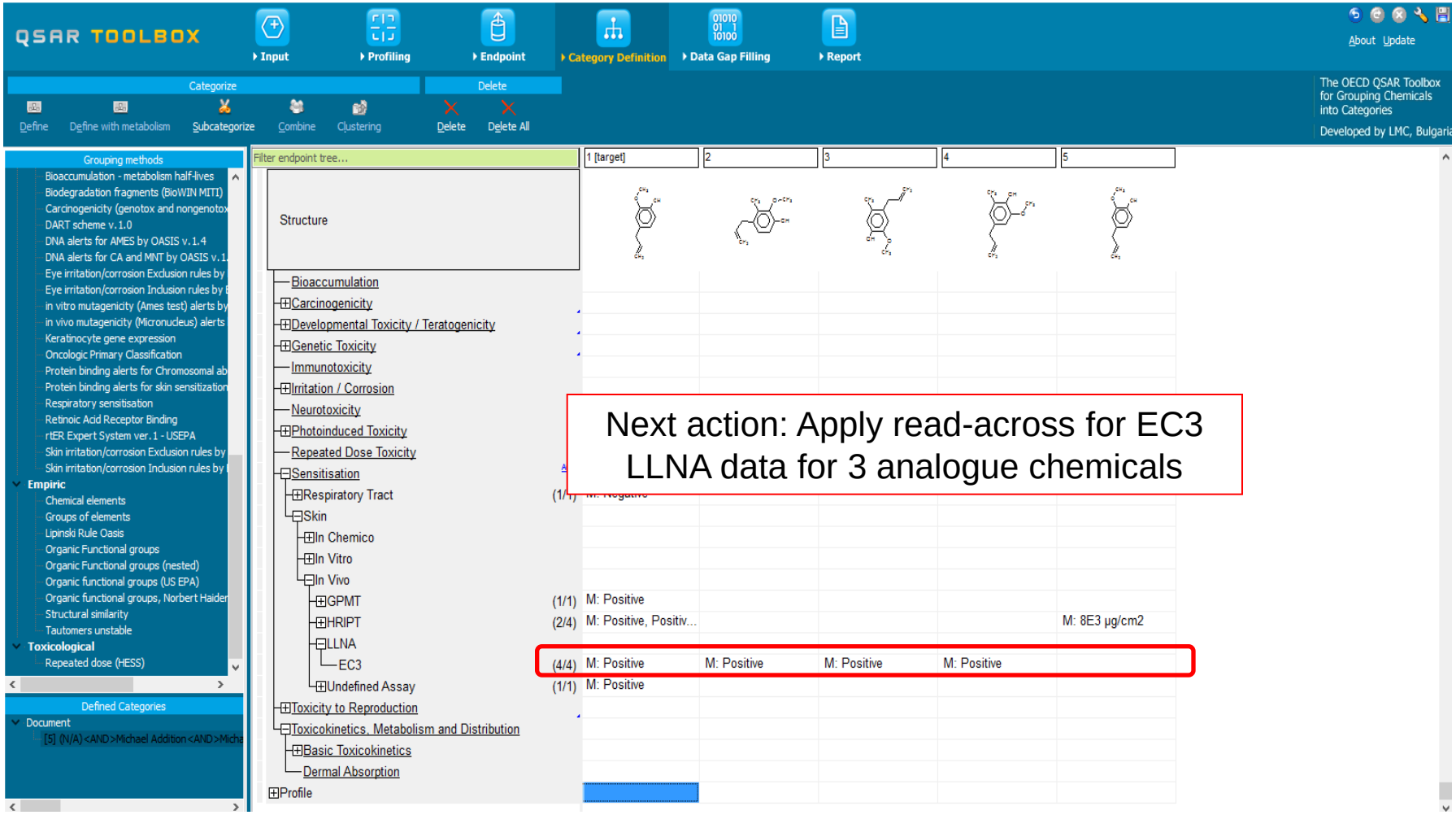
Categorization applying metabolism

Profile statistic



All metabolites have same distribution of the protein binding alets after metabolic transformation

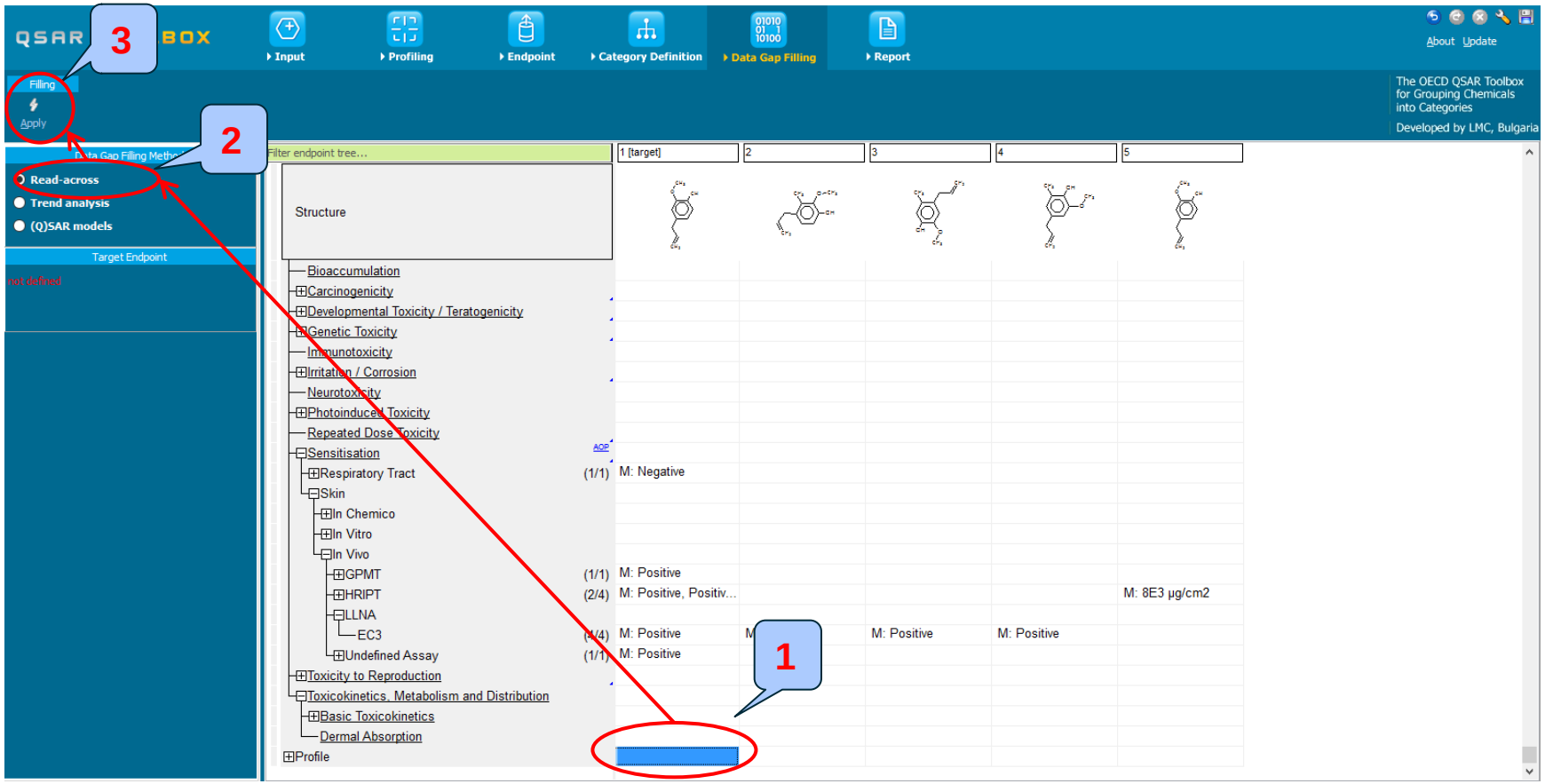
Categorization applying metabolism



Outlook

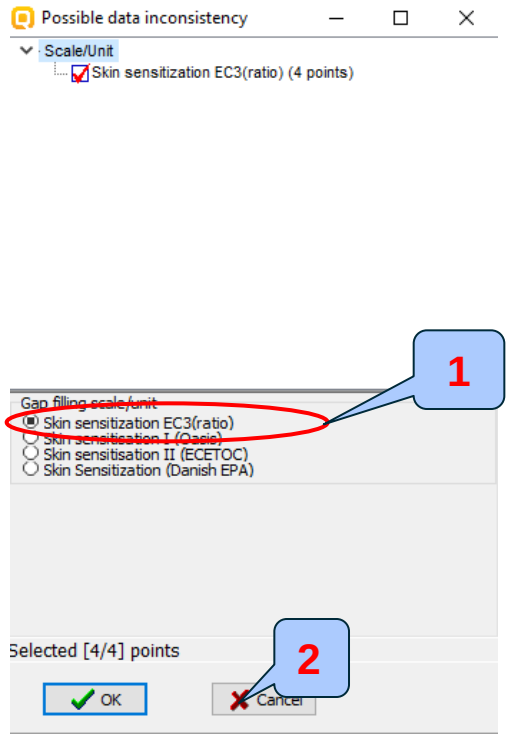
- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - Categorization applying metabolism
  - **Data gap filling handling metabolism of the target chemical**

Data gap filling
Apply Read across



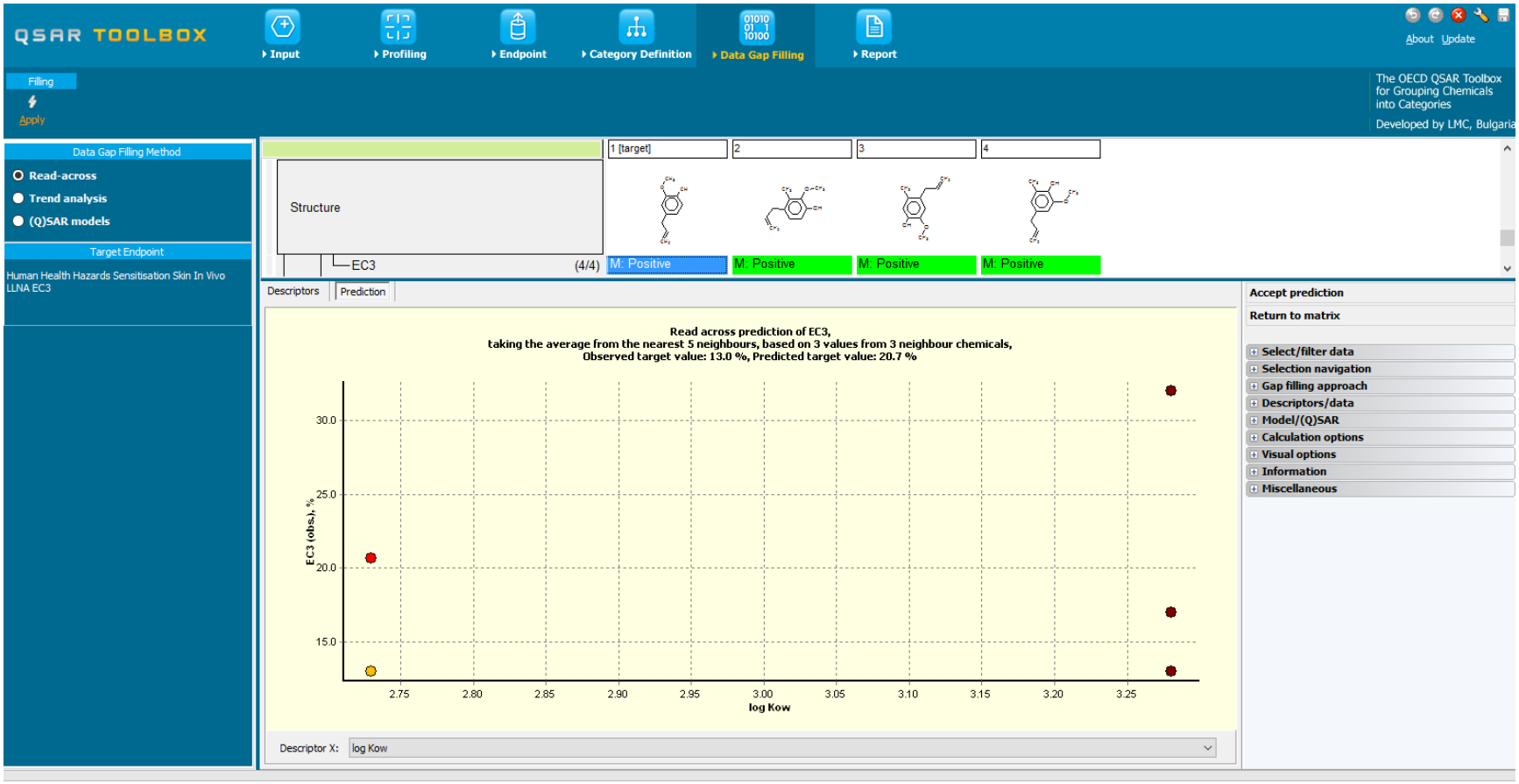
1. **Click** on the cell corresponding to "Sensitization>>Skin>>In Vivo>>LLNA>>EC3" for the target chemical 2. **Select** "Read-across" 3. **Click** "Apply"

Data gap filling
Scale definition



1. **Select** scale "Skin sensitisation EC3 (ratio)"
2. **Click** "OK"

Data gap filling
Read-across



Initial graph without any subcategorizations

Data Gap Filling
Subcategorizations

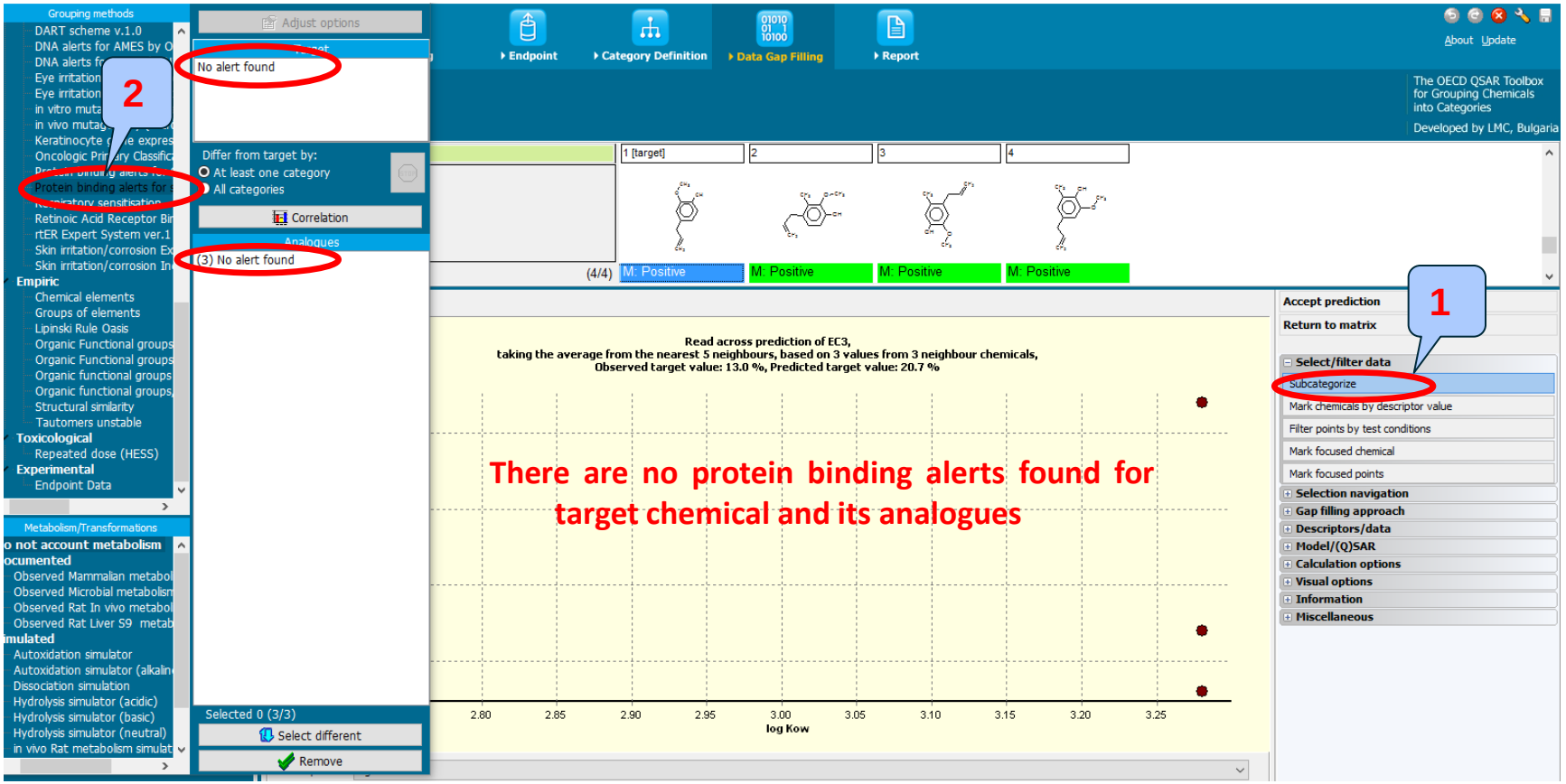
In this second data gap filling, the following subcategorizations are applied (see slide 44):

- Protein binding alerts for skin sensitization by OASIS v1.4 (subcategorization 1)
- Protein binding alerts skin sensitization by OASIS v1.4 taking into account autoxidation metabolism (subcategorization 2)

See next screen shots.

Data gap filling

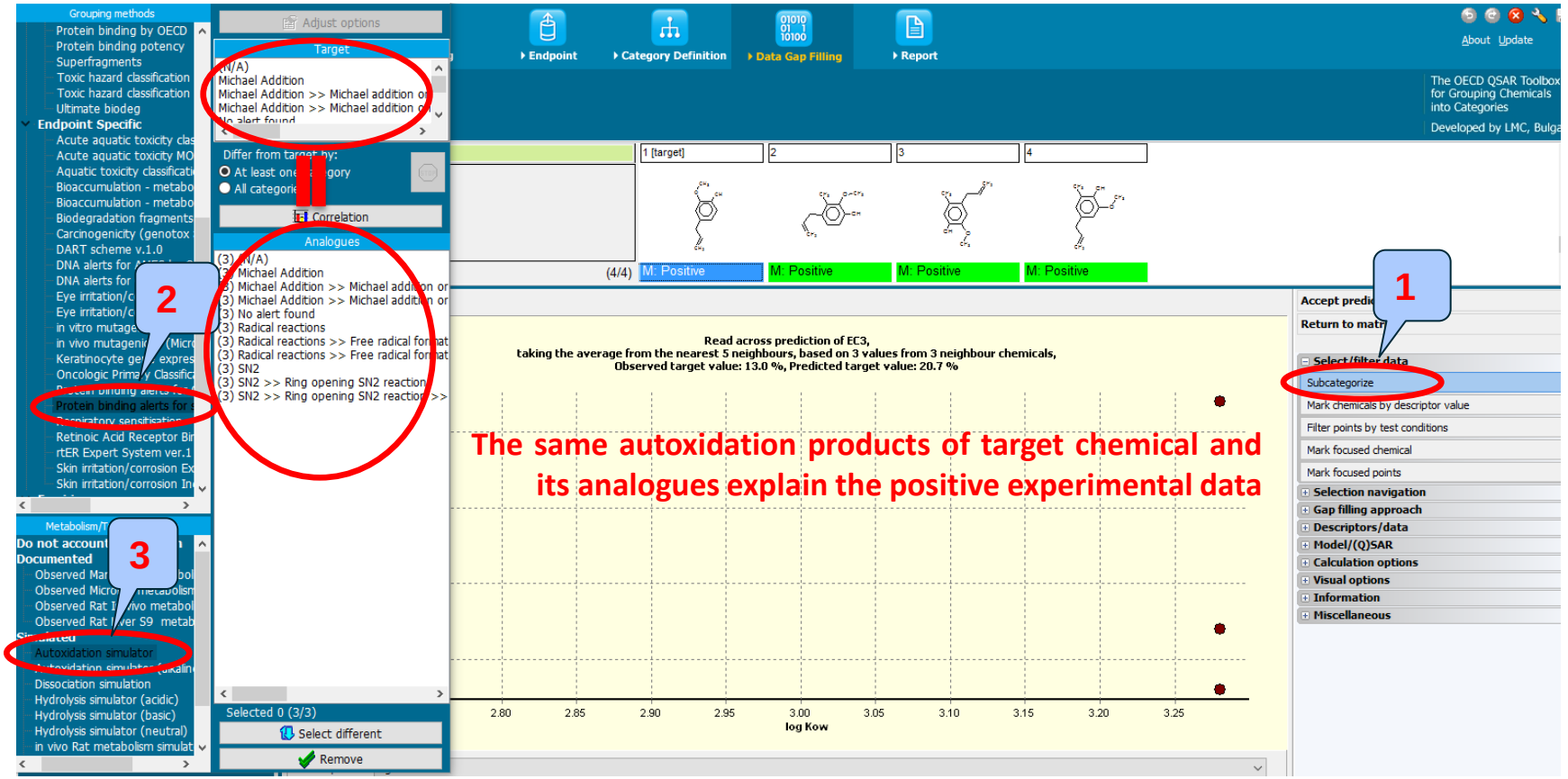
Subcategorization 1: Protein binding alerts for skin sensitization by OASIS v1.4



1. **Open** "Select filter data/subcategorize";
2. **Select** "Protein binding alerts for skin sensitization by OASIS v1.4"

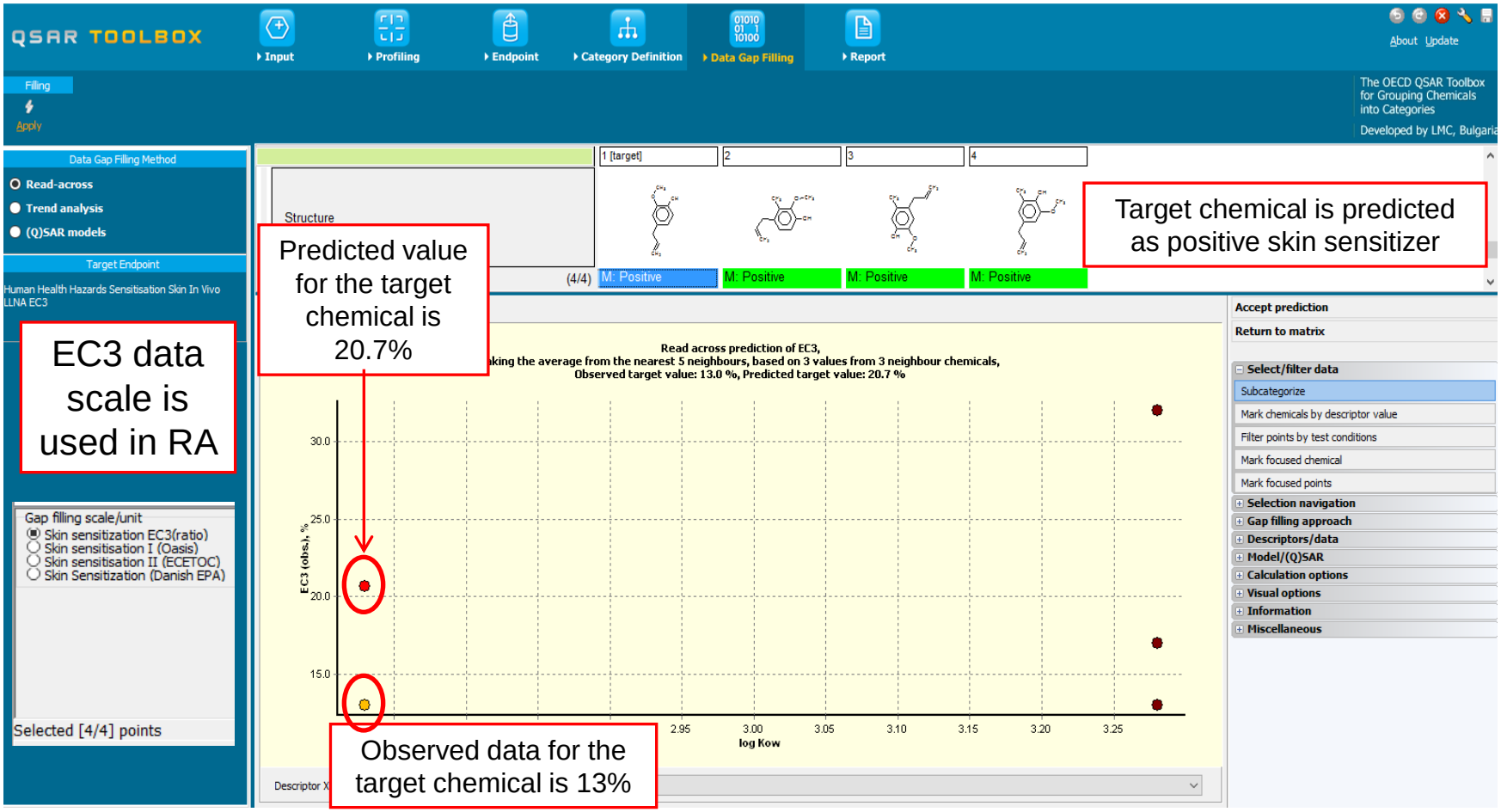
Data gap filling

Subcategorization 2: Protein binding alerts for SS when AO is taken into account

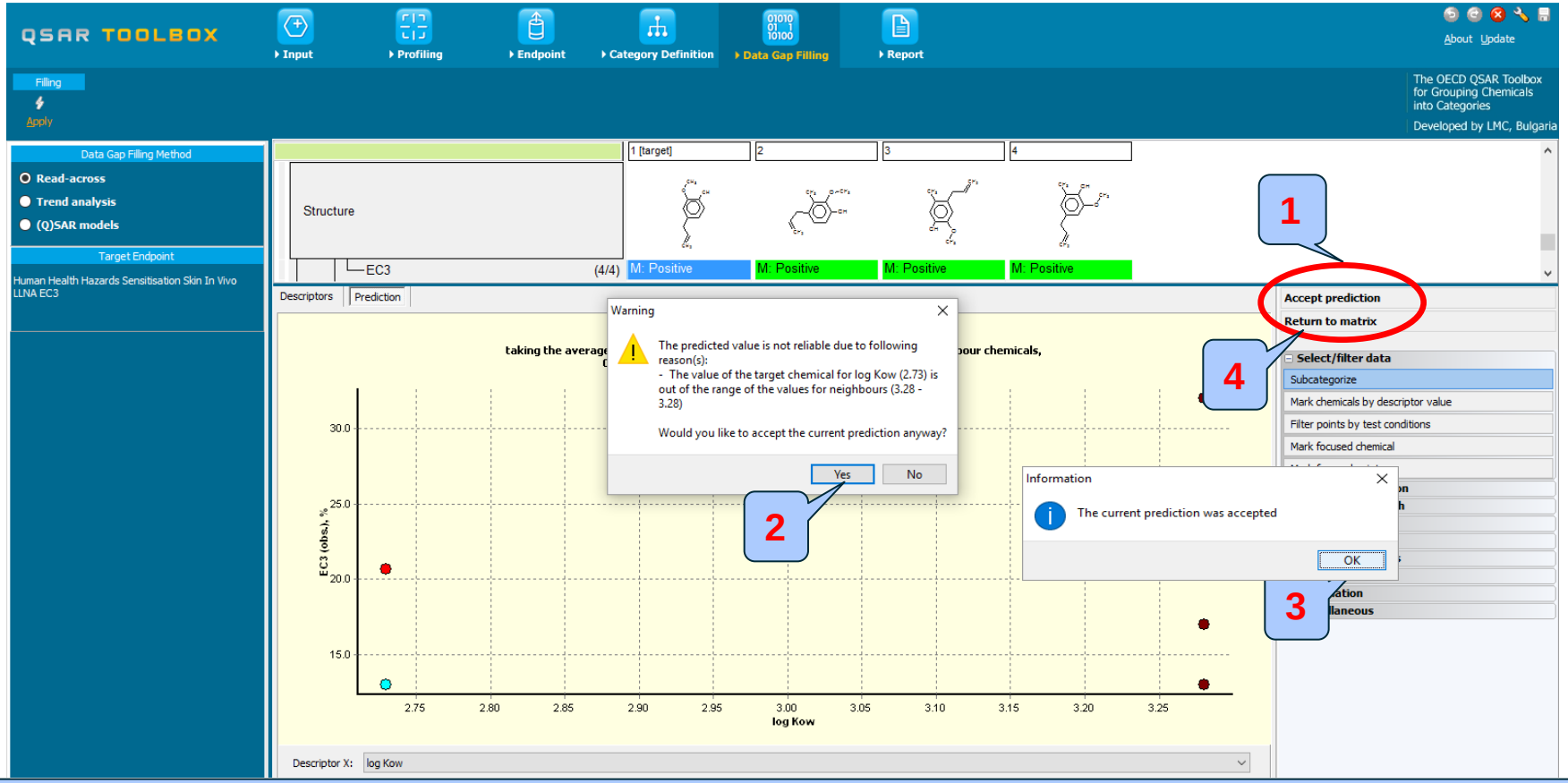


1. **Open** "Select filter data", **click** "Subcategorize"; 2. **Select** "Protein binding alerts for skin sensitization by OASIS v1.4";
3. **Select** "Autoxidation simulator"

Data gap filling results



Data gap filling results

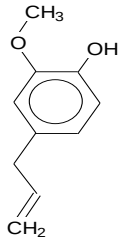


1.**Click** "Accept prediction"; 2. A message informing the user that the target is out of parametric domain appears. **Click** "Yes"; 3. **Click** "OK" on the appeared message 4. **Click** "Return to matrix"

Recap

Parent

Eugenol
CAS# 97-53-0



Protein binding alert
(Protein binding by OASIS)

No alert found

Experimental data

LLNA
Strong sensitizer

Data gap filling

No protein binding alerts

Positive RA prediction

How to explain positive RA ?

Autoxidation Simulator/Skin metabolism

Protein binding alert found for package of metabolites

Categorization with metabolism

Identifying protein binding analogues of the target taking into account its metabolic activation

Positive Protein binding alerts

Positive RA prediction

Outlook

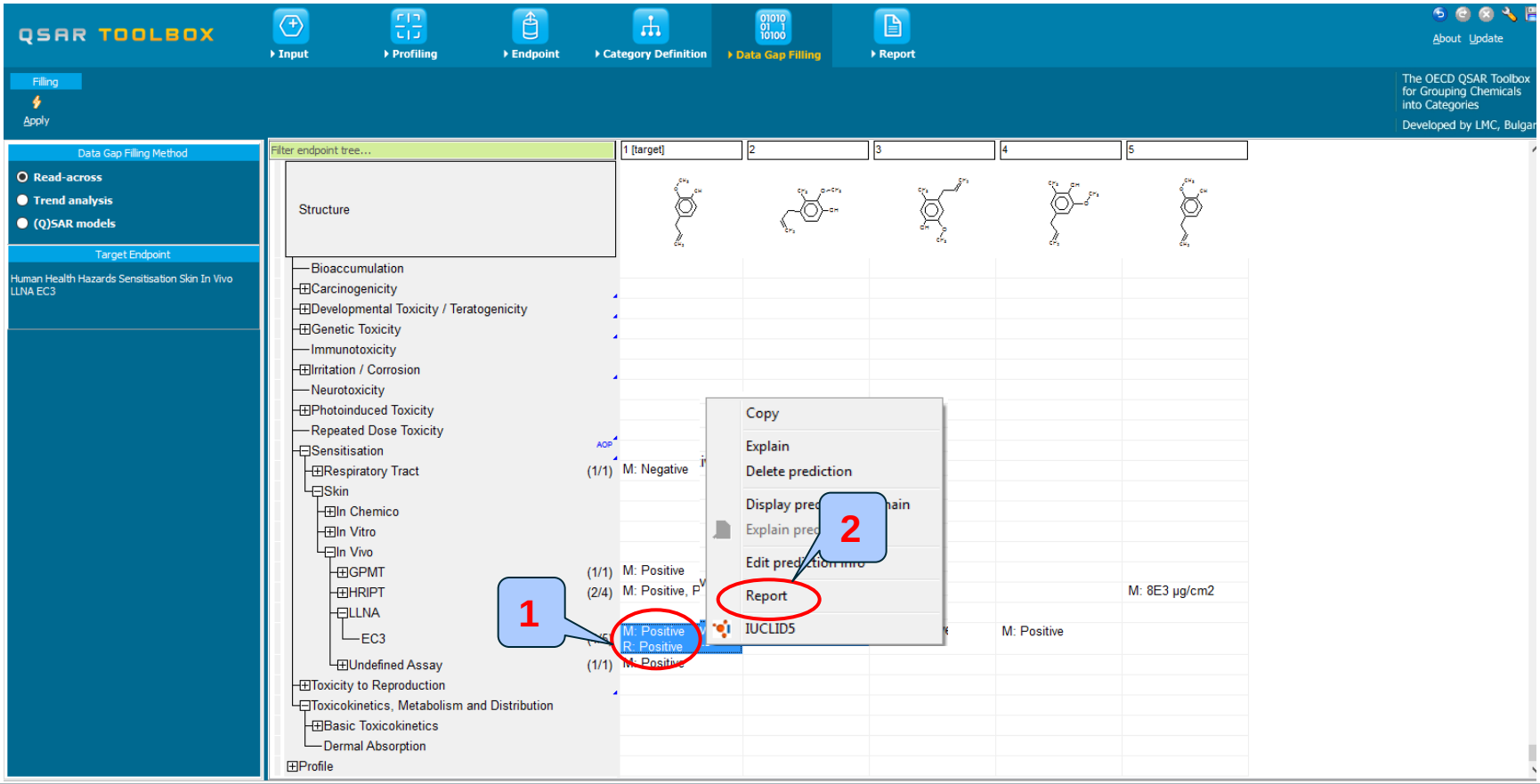
- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - Categorization applying metabolism
  - Data gap filling handling metabolism of the target chemical
  - **Report**

Report

- The report module allows you to generate a report on the predictions obtained with the Toolbox. This module contains predefined report templates as well as a template editor with which users can define their own user defined templates. The report can then be printed or saved in different formats.

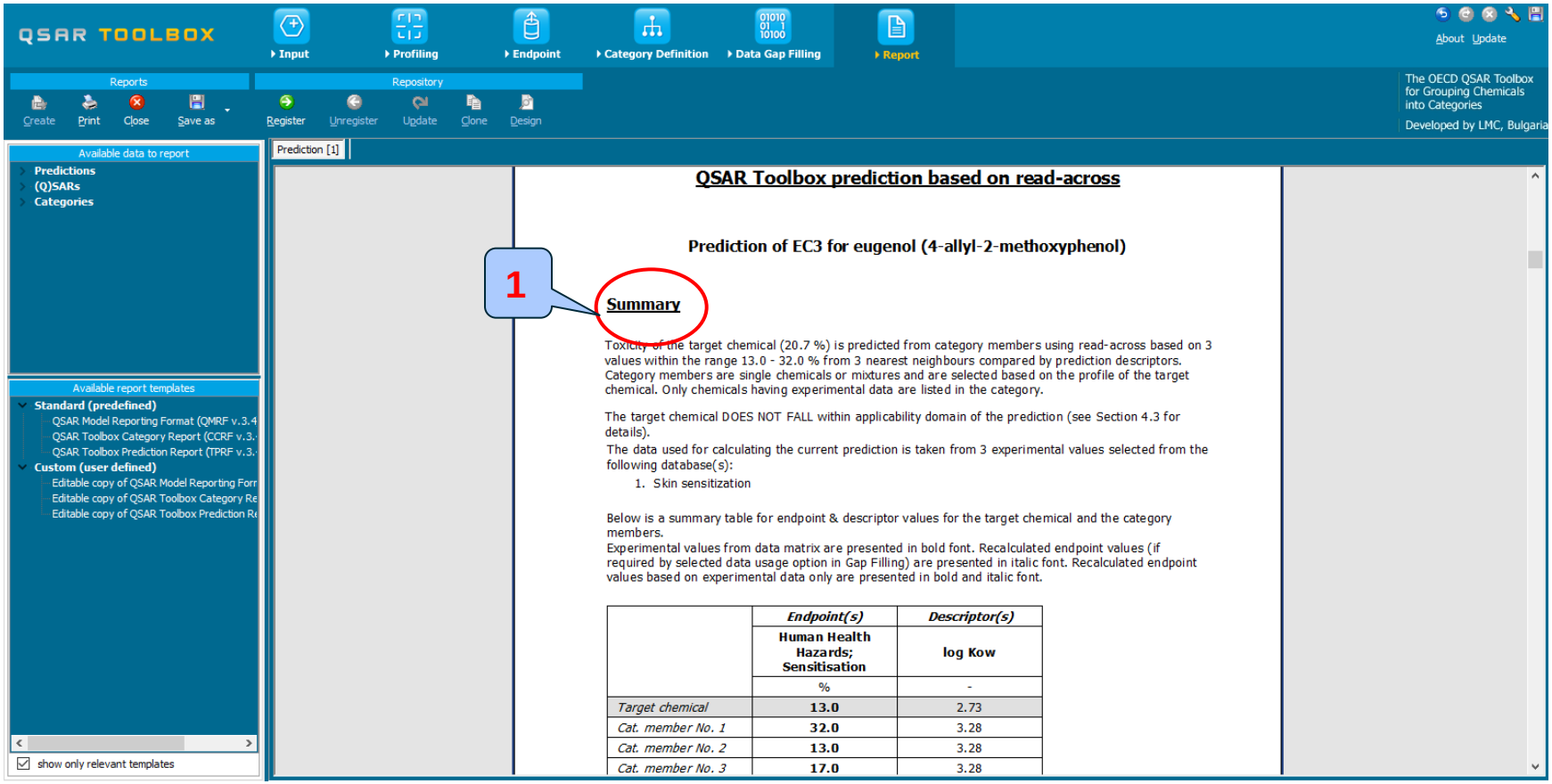
- Generating the report is shown on next screenshots.

Report



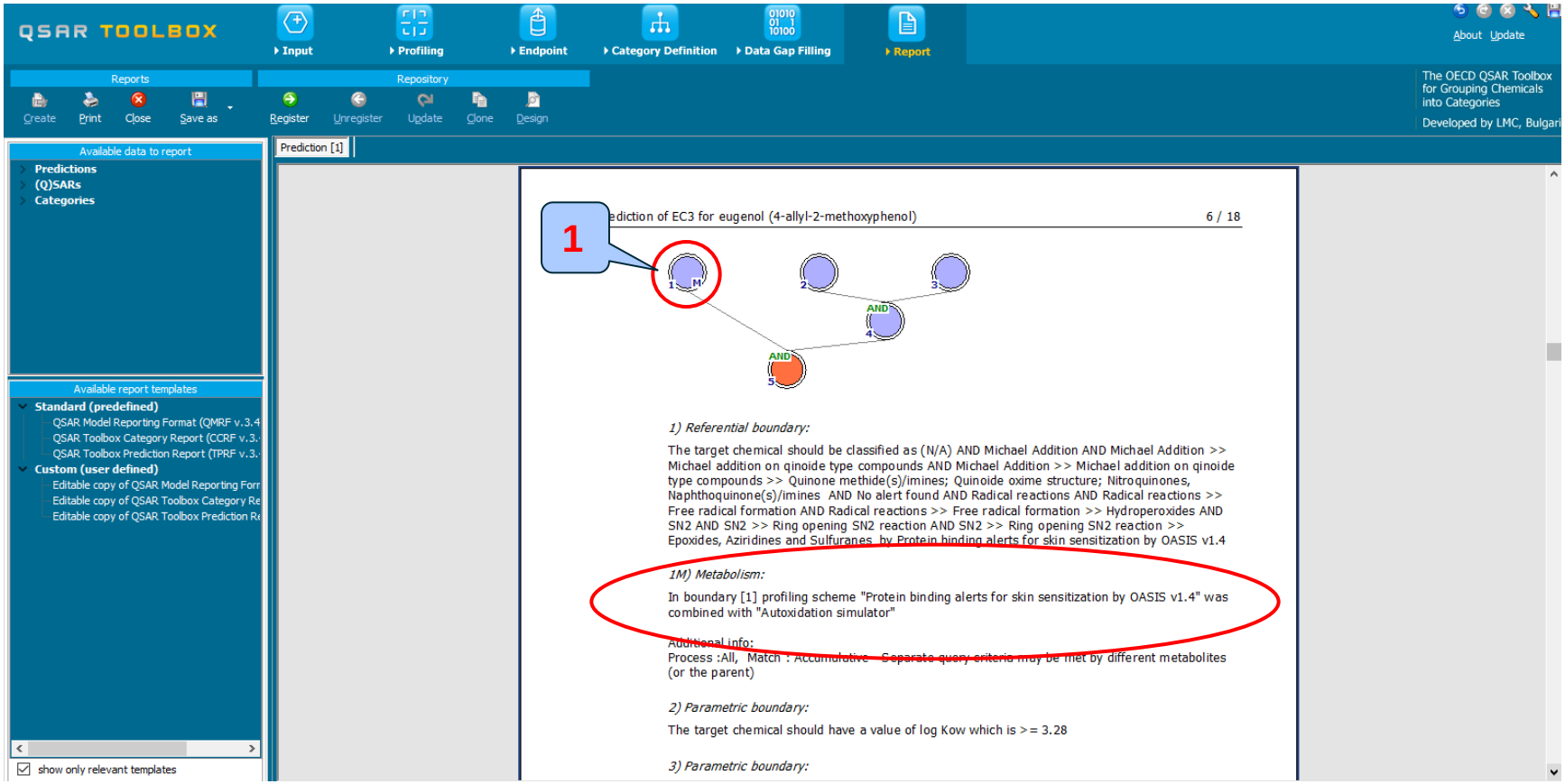
1. **Select** prediction
2. **Right click** and **Select** "Report"

Report



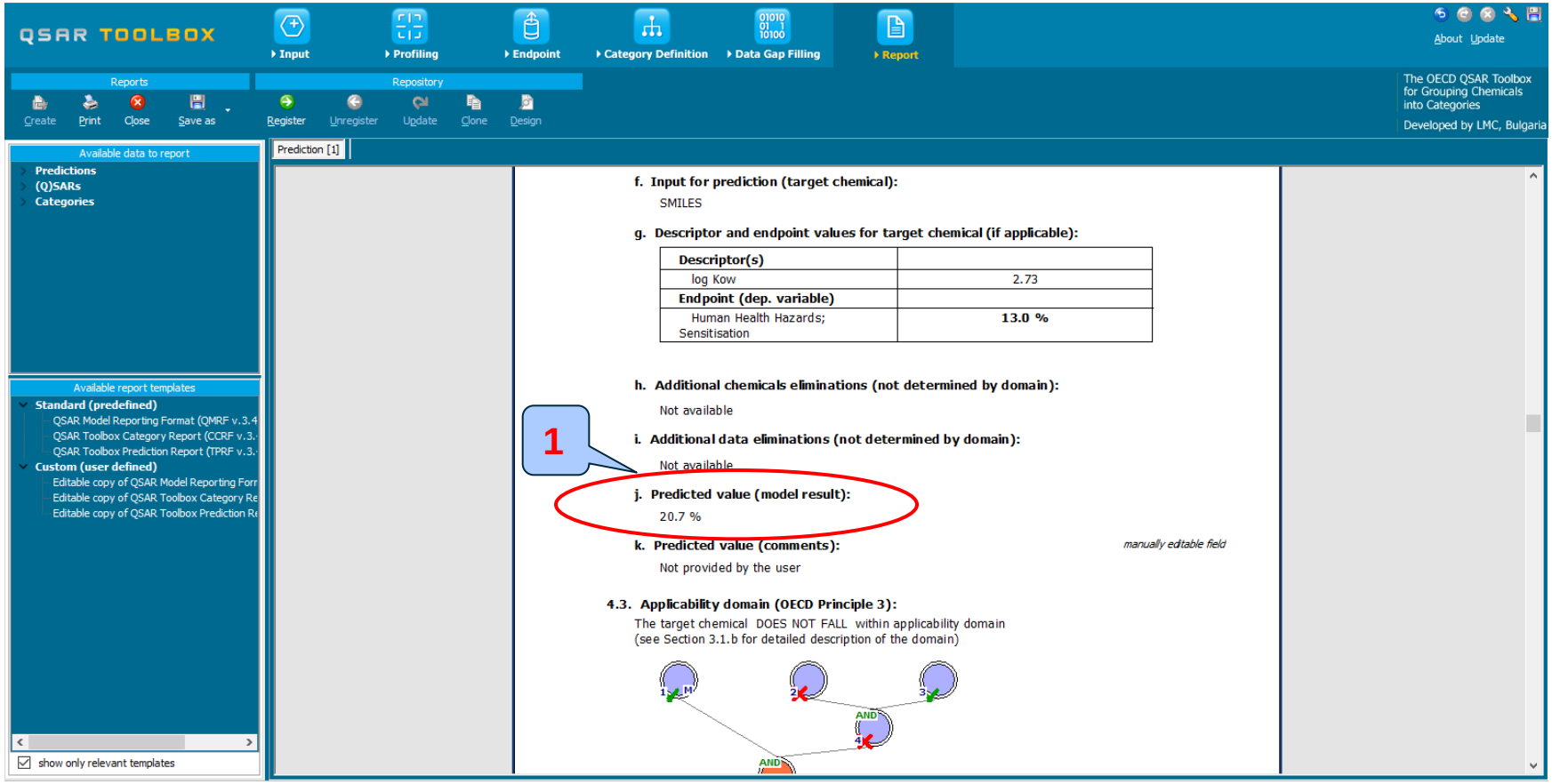
1. Summary information for prediction

Report



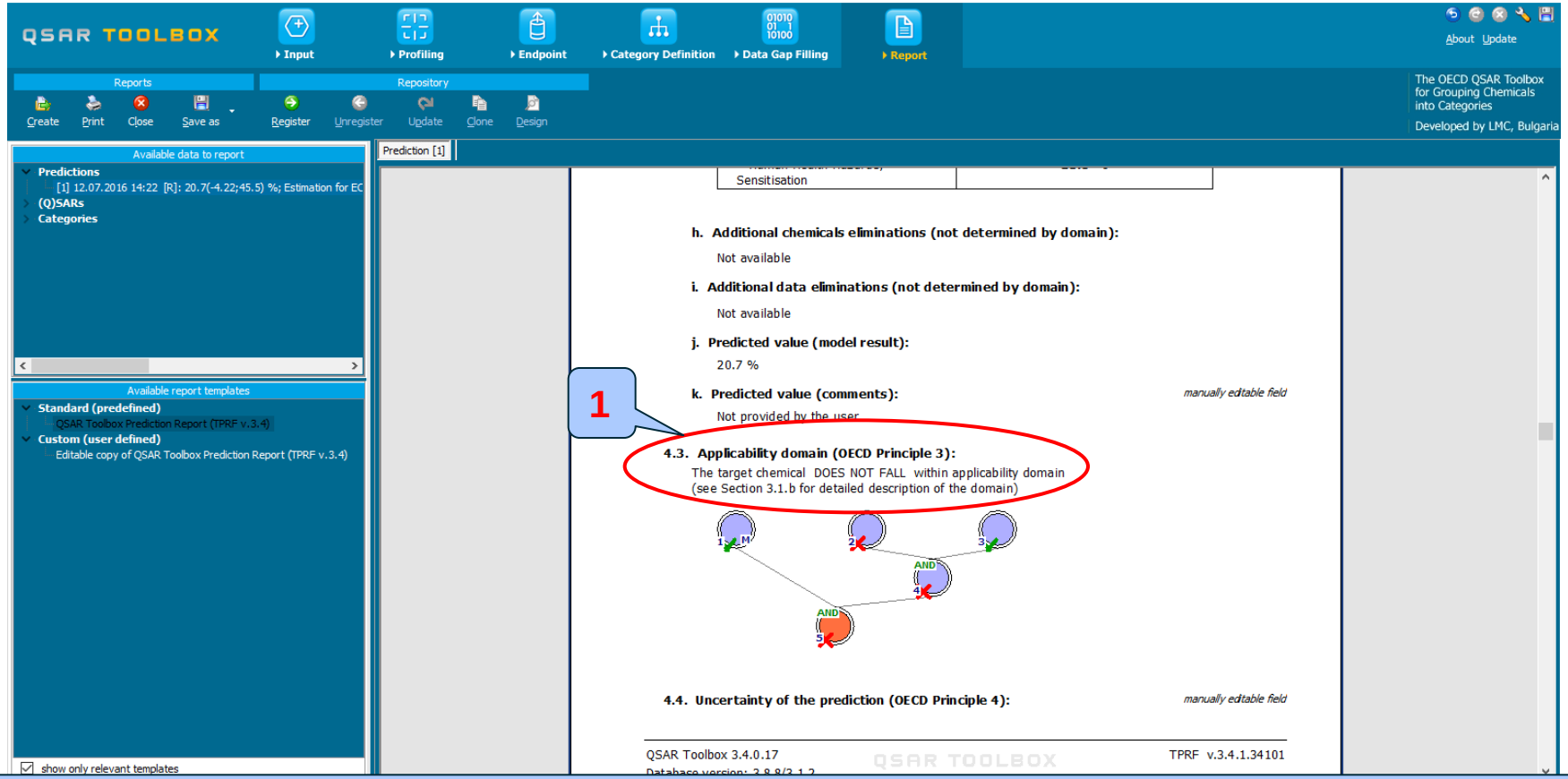
1. Information that metabolism was taken into account when predicting skin sensitization is available

Report



1. Predicted value

Report



1. Applicability domain

The target chemical is "Out of domain", because does not fall within parametric range of Log Kow[3.28-4.75]

Outlook

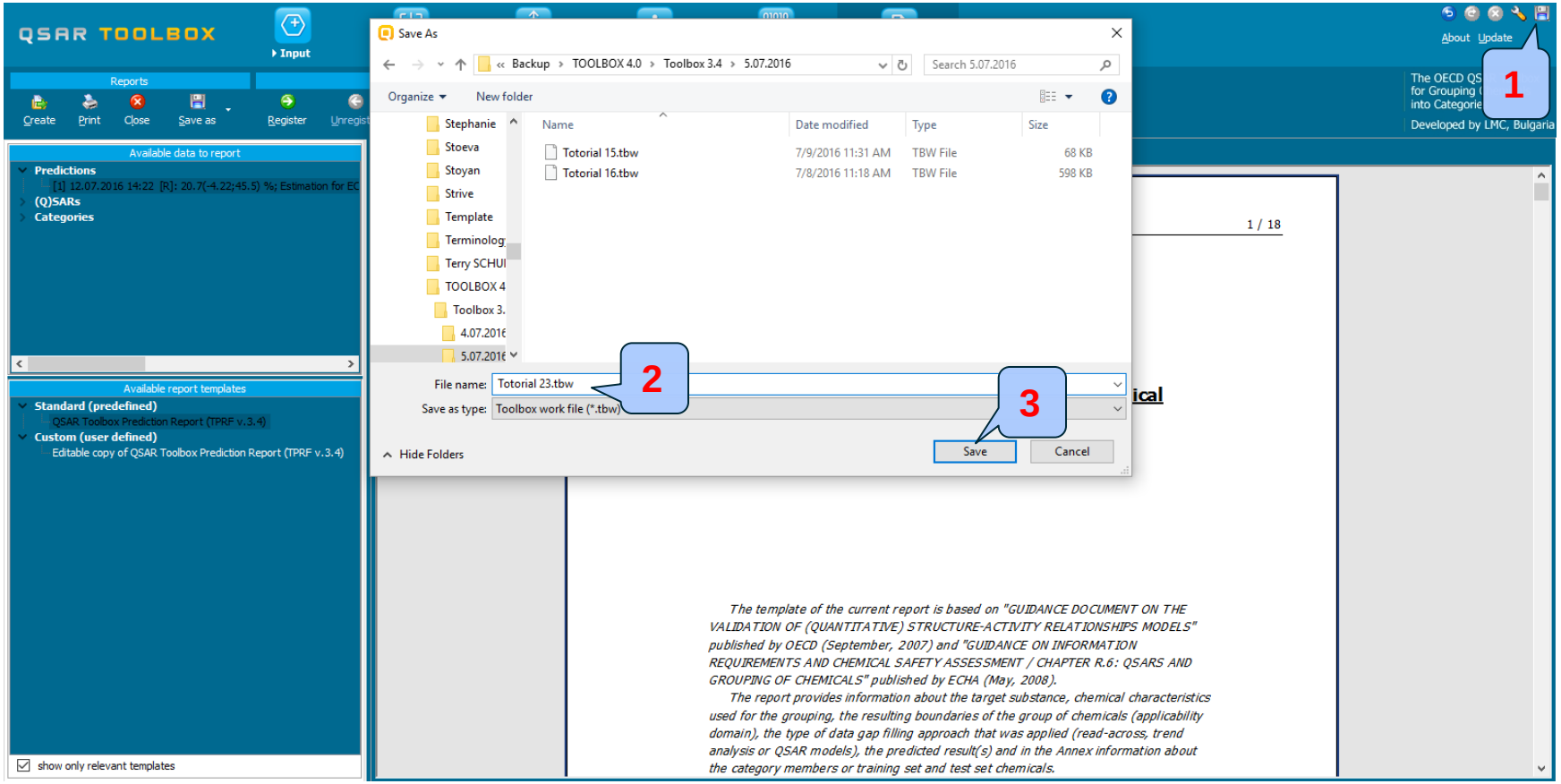
- Background
- Objectives
- The exercise
- **Workflow**
  - Input
  - Profiling
  - Endpoint
  - Categorization
  - Data gap filling without taken into account metabolism
  - Categorization applying metabolism
  - Data gap filling handling metabolism of the target chemical
  - Report
  - **Save the prediction**

Saving the prediction result

- This functionality allow storing/restoring the current state of Toolbox documents including loaded chemicals, experimental data, profiles, predictions etc, on the same computer. The functionality is implemented based on saving the sequence of actions that led to the current state of the Toolbox document and later executing these actions in the same sequence in order to get the same result(s).

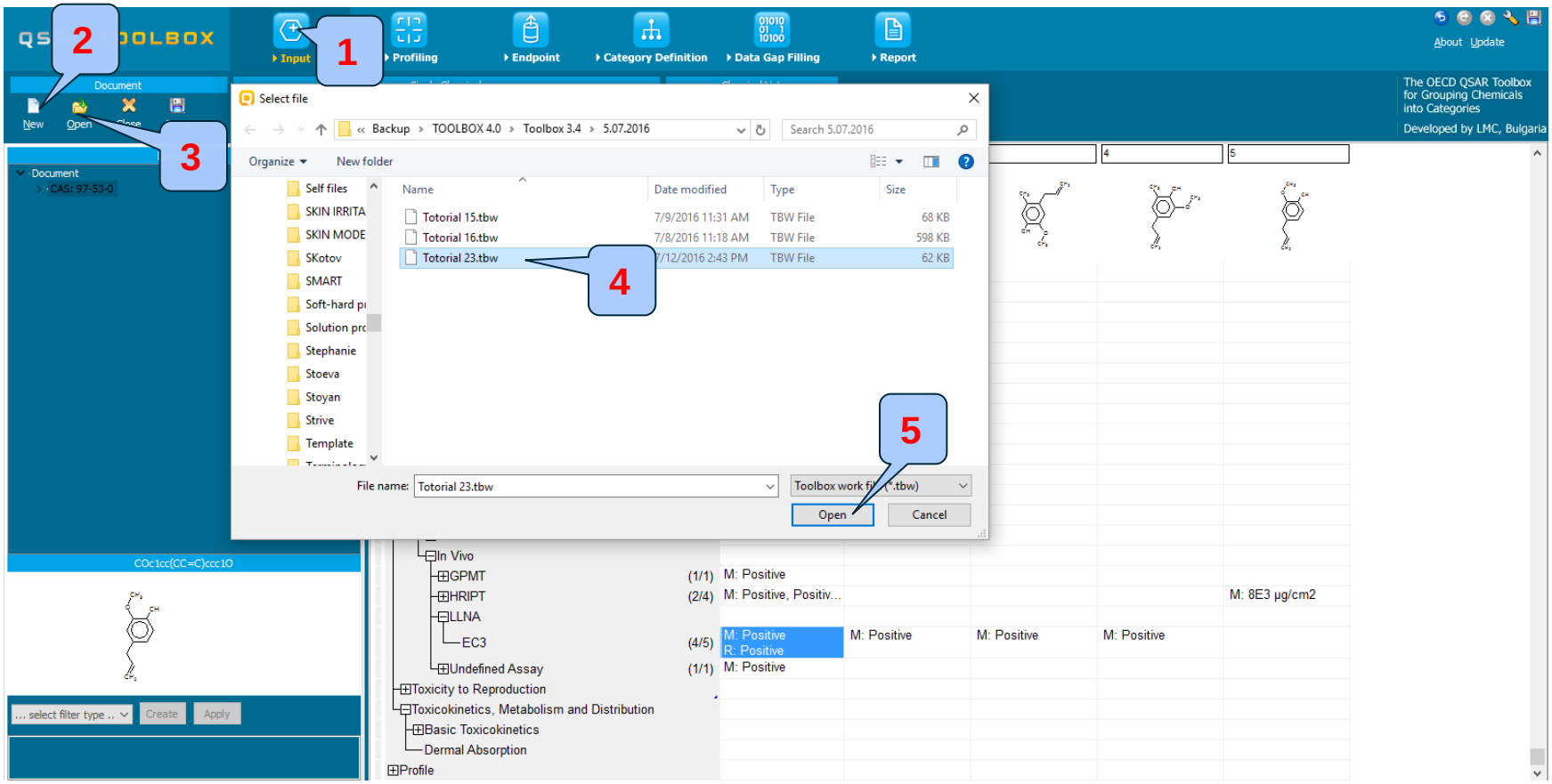
- Saving/Loading the file with TB prediction is shown on next screenshots.

Saving the prediction result



1. **Click** on "Save" button; 2. **Browse** and **put** name of the file; 3. **Click** Save button

Open saved file



Once the file has been saved 1. **Go** to "Input"; 2.**Create** new document 3.**Click** "Open"; 4. **Browse** and **select the file**; 5. **Click** "Open" button