QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

OECD QSAR Toolbox v.3.4

Step-by-step example of how to build a user-defined profiling scheme

Outlook

- **Background**
- Objectives
- Profiling
- The exercise

Background

- This is a step-by-step presentation designed to provide guidance to users of the Toolbox on how to create their own profiling scheme.

Outlook

- Background
- **Objectives**
- Profiling
- The exercise

Objectives

- **This presentation demonstrates how to build a new profiling scheme including the:**

  - naming of the new scheme
  - building a category by defining its boundaries
  - saving the new profiler

Outlook

- Background
- Objectives
- **Profiling**
- The exercise

Profiling
Overview

- As you are aware “Profiling” refers to the electronic process of retrieving relevant information on a compound which is stored in the Toolbox, other than fate and toxicity data.
- The Toolbox has many predefined profilers but it also allows the user to development new profilers.

Outlook

- Background
- Objectives
- Profiling
- **The exercise**

The Exercise

In this example we build a profiler that identifies chemicals:

- that are aldehydes (rule 1)
- that can react with proteins by "Schiff base formation" (rule 2), but
- that do not react with proteins by "Michael-type nucleophilic addition" (rule 3)
- which also have the fragment C(=O)(O)c1ccccc1 in their structure (rule 4), and
- that have a value of Log KOW between 1 and 7 (rule 5).

The Exercise
Start building a new profiler

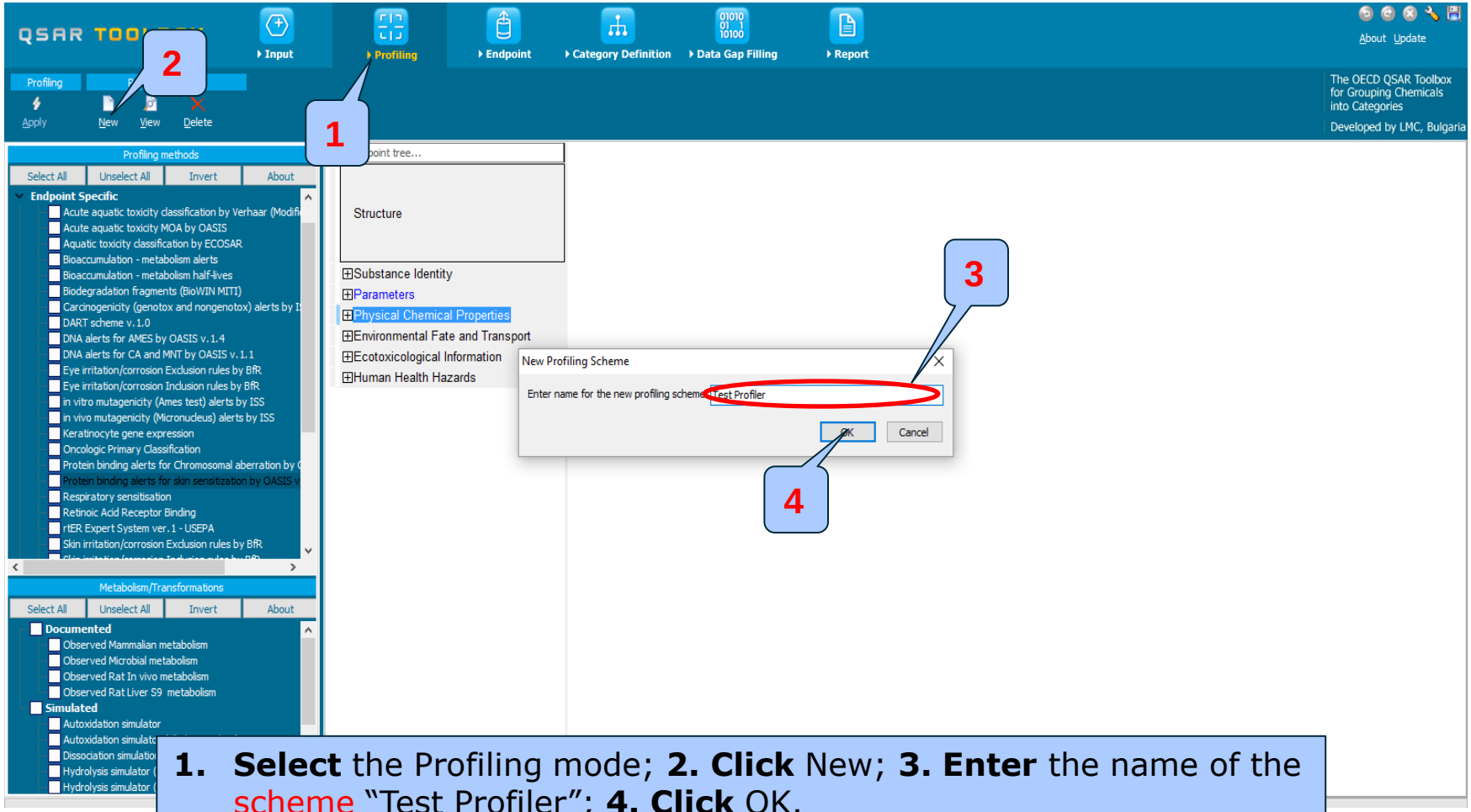
We are going to create a new profiling scheme:

- Open the Toolbox.
- Move to the Profiling module

(see next screen shot).

Building of a new profiler

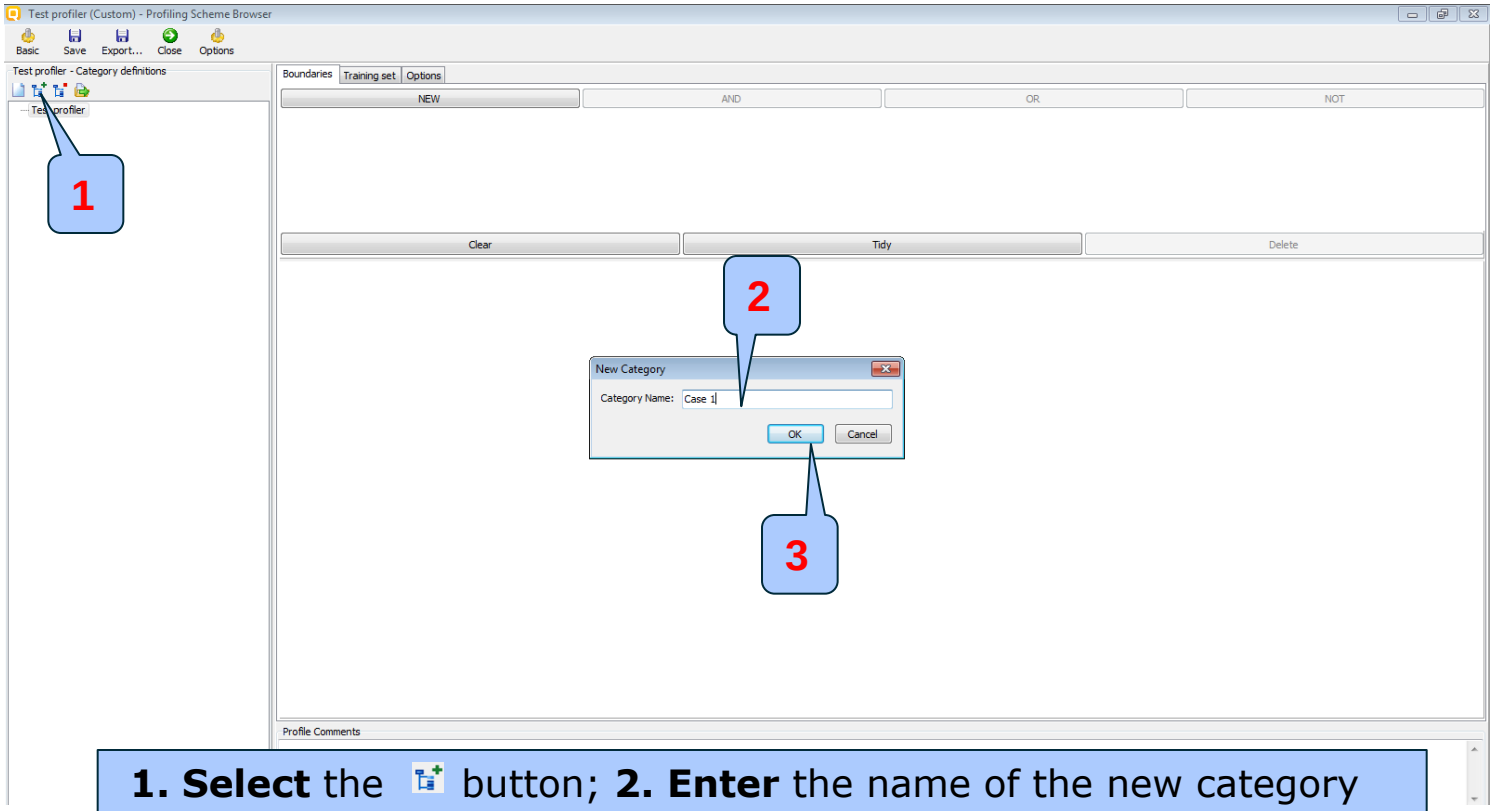
Define the name of the new profiler



1. Select the Profiling mode; **2. Click** New; **3. Enter** the name of the scheme "Test Profiler"; **4. Click** OK.

Building of a new profiler

Add a new category within the profiler



1. Select the button; **2. Enter** the name of the new category "Case 1"; **3. Click** OK.

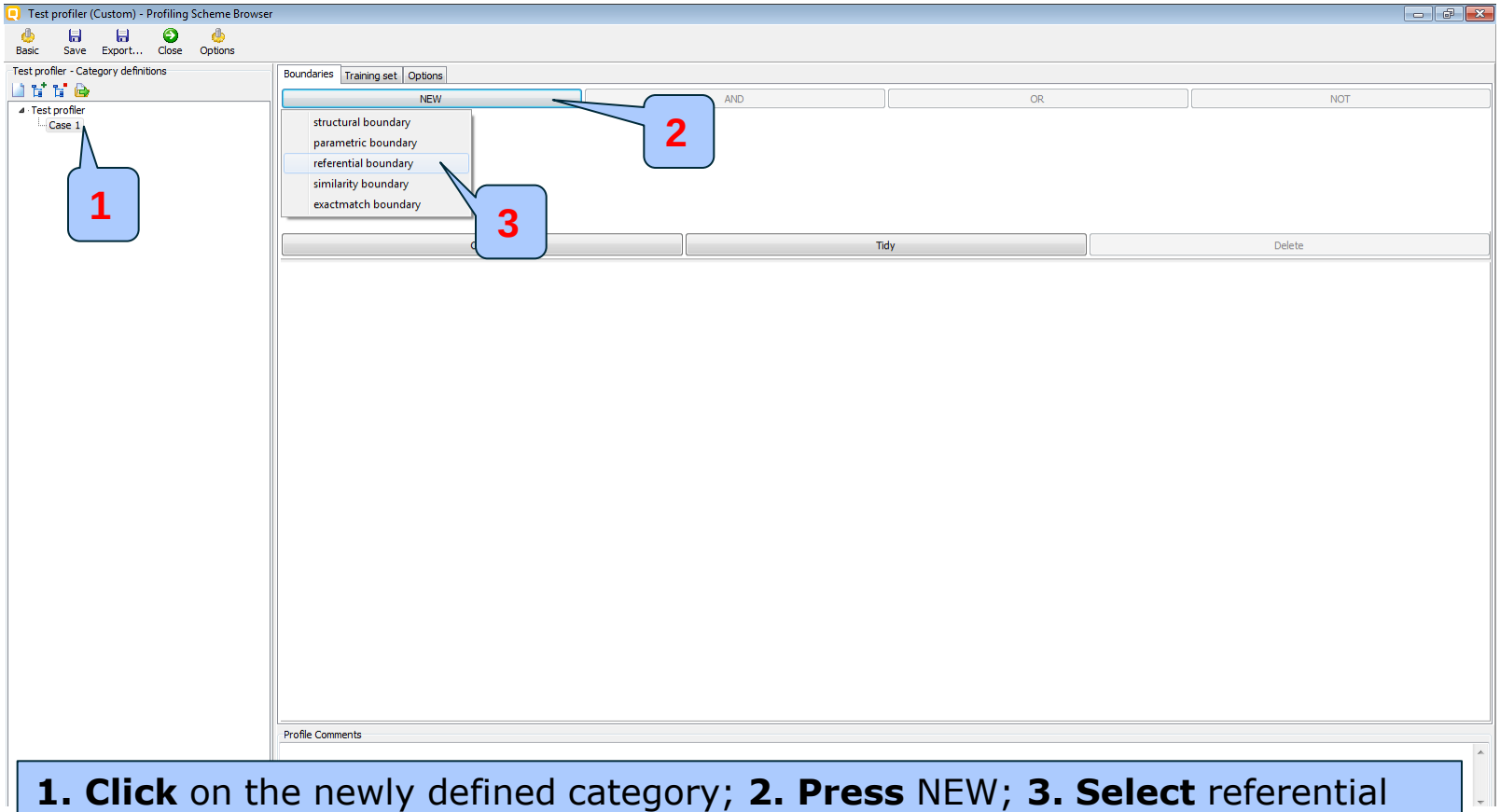
Building of a new profiler

Building the category definition – rule 1

To specify aldehydes, include a referential boundary making use of the predefined category definition "Aldehydes" within the Organic functional groups profiler.

Building of a new profiler

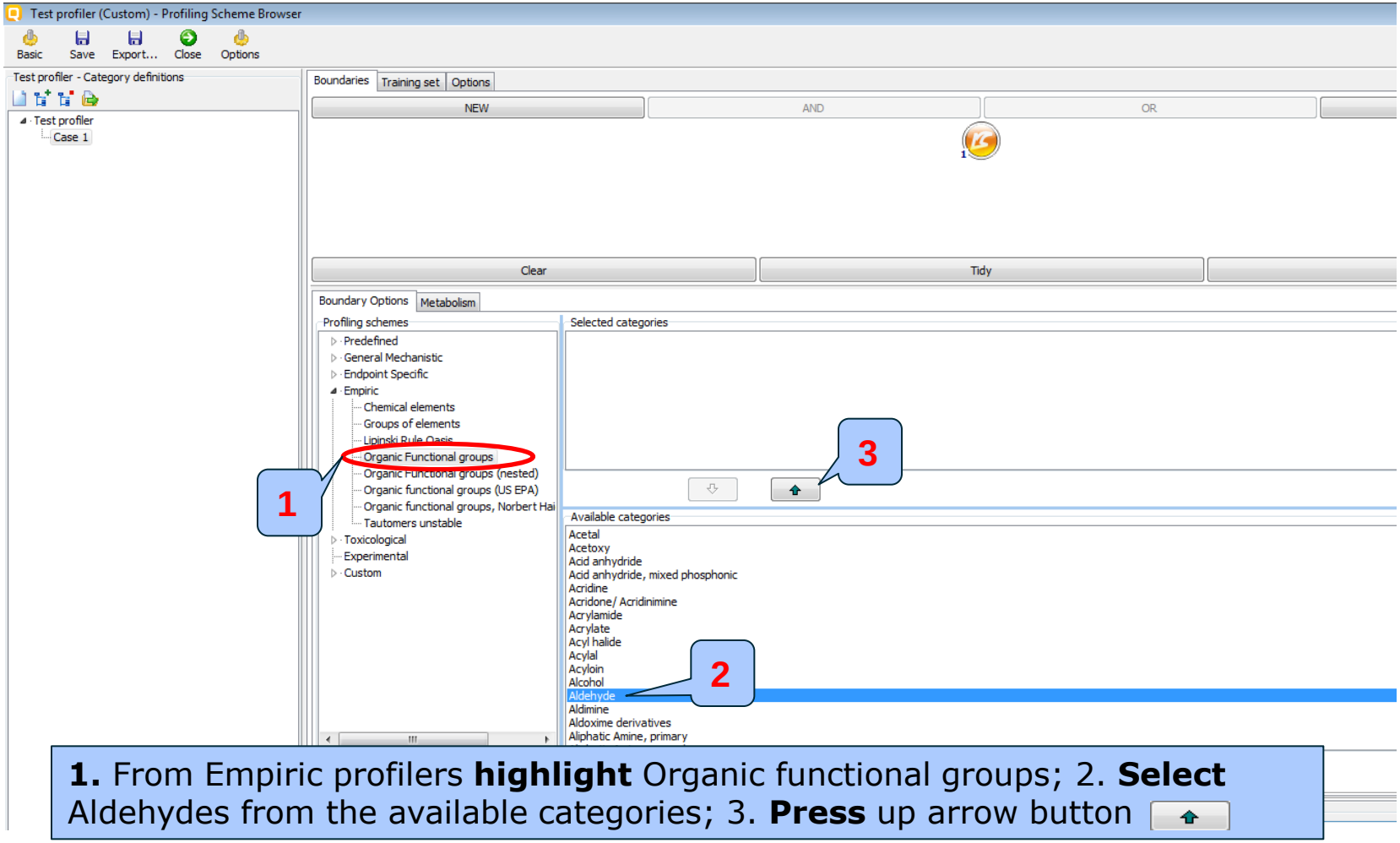
Building the category definition – rule 1



1. Click on the newly defined category; **2. Press** NEW; **3. Select** referential boundary.

Building of a new profiler

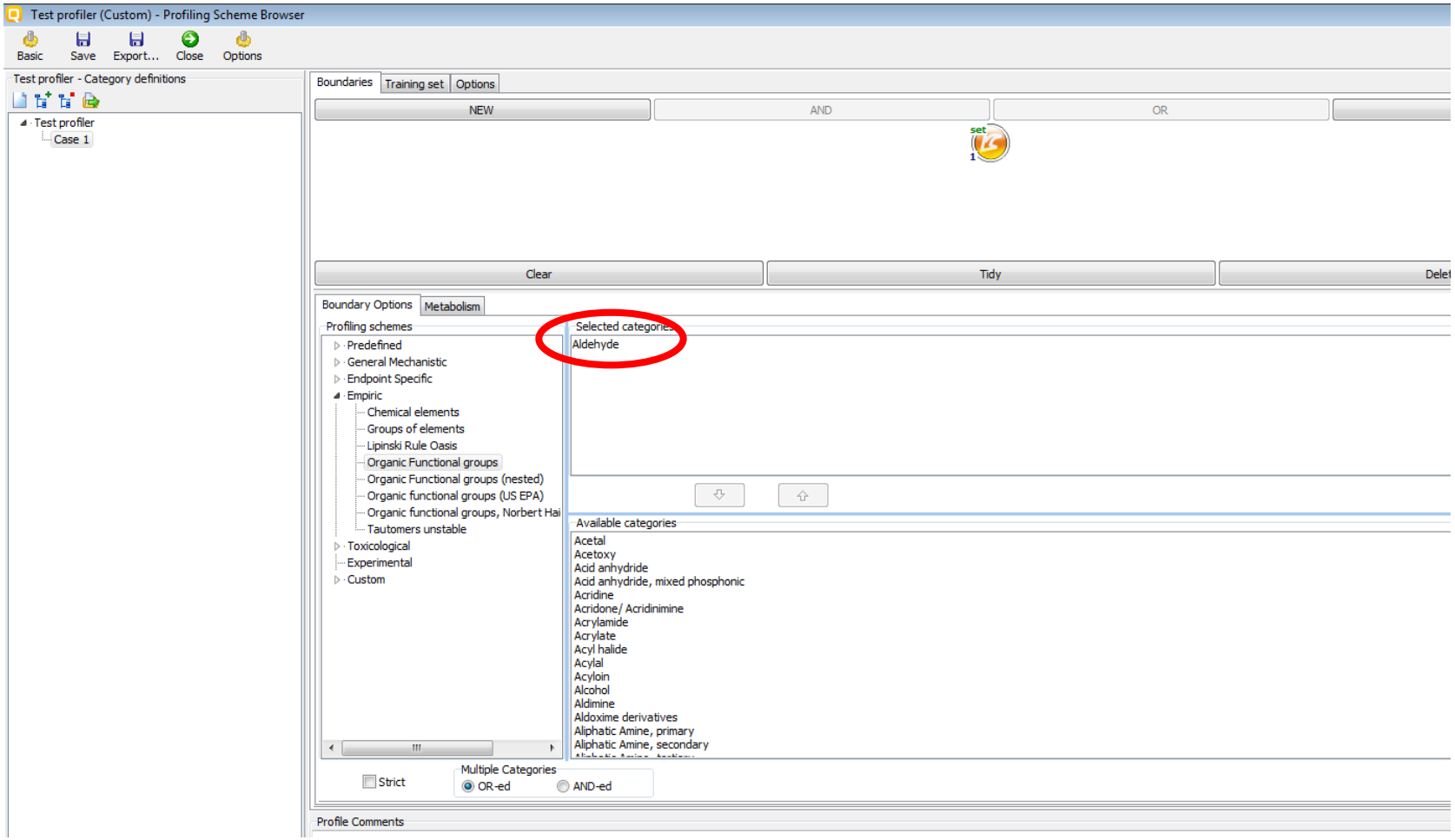
Building the category definition – rule 1



1. From Empiric profilers **highlight** Organic functional groups; 2. **Select** Aldehydes from the available categories; 3. **Press** up arrow button

Building of a new profiler

Building the category definition – rule 1



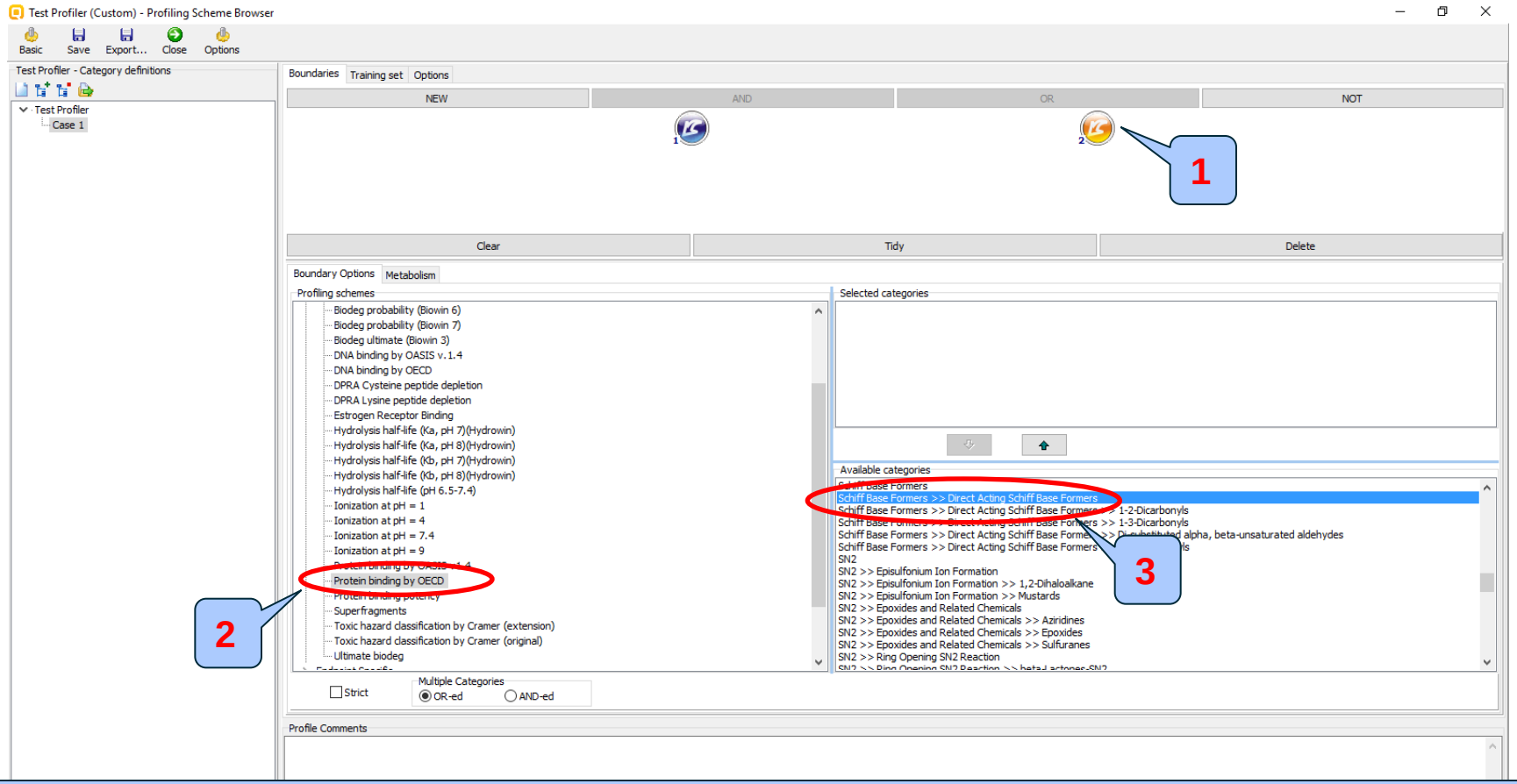
Building of a new profiler
Restriction of the category definition

To restrict the category definition by mechanism, add two additional referential boundaries:

- the first one specifies chemicals that can react with proteins by forming a Schiff base (rule 2) according to Protein binding by OECD.
- the other one specifies chemicals that do NOT react with proteins by Michael-type nucleophilic addition (rule 3) according to Protein binding by OECD.

Building of a new profiler

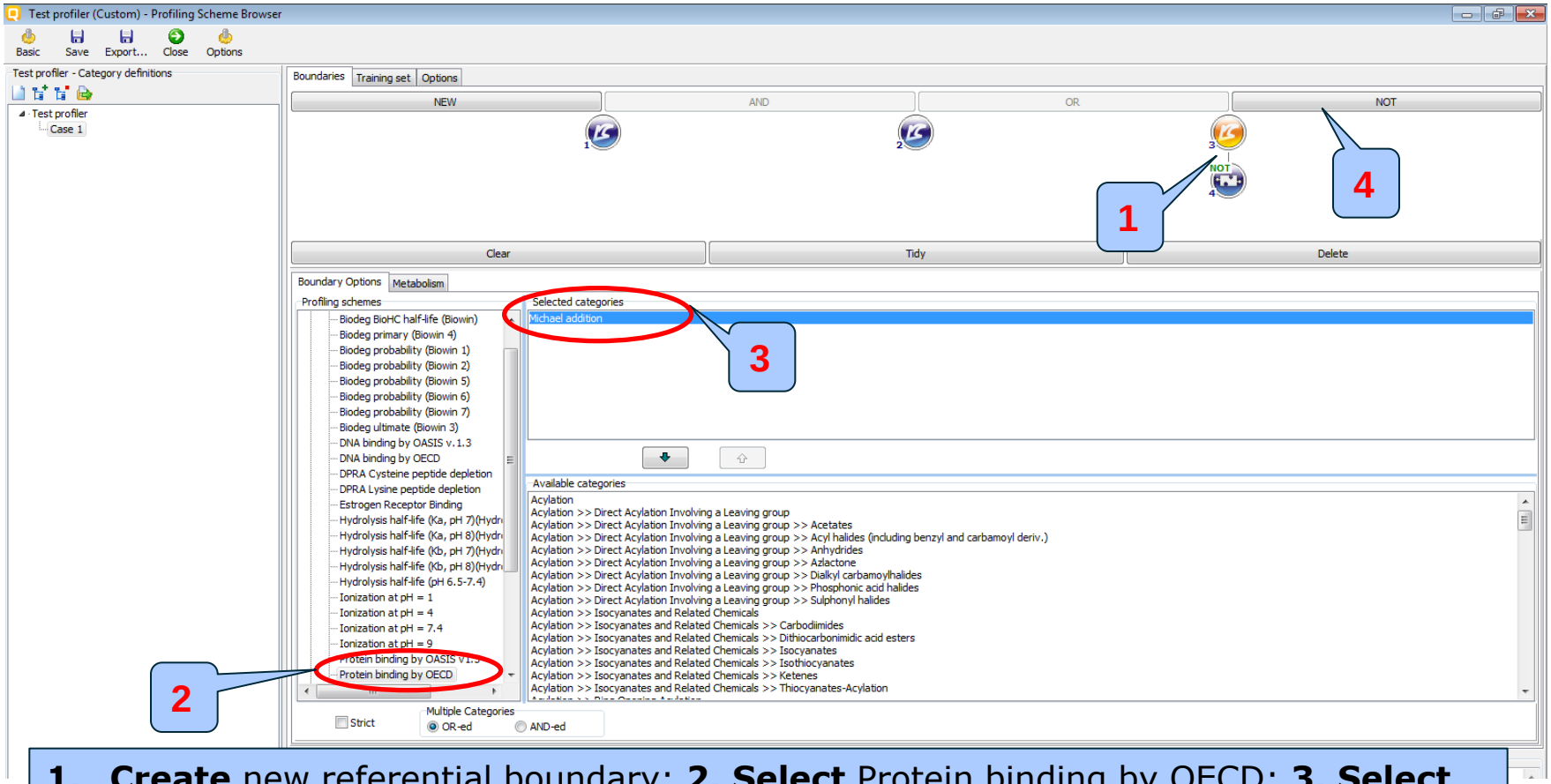
Building the category definition – rule 2



1. **Create** new referential boundary; **2.** From the General mechanistic profilers **select** Protein binding by OECD; **3. Select** Schiff base formers>>Direct Acting Schiff Base Formers category from the panel with available categories and move it to the panel Selected categories

Building of a new profiler

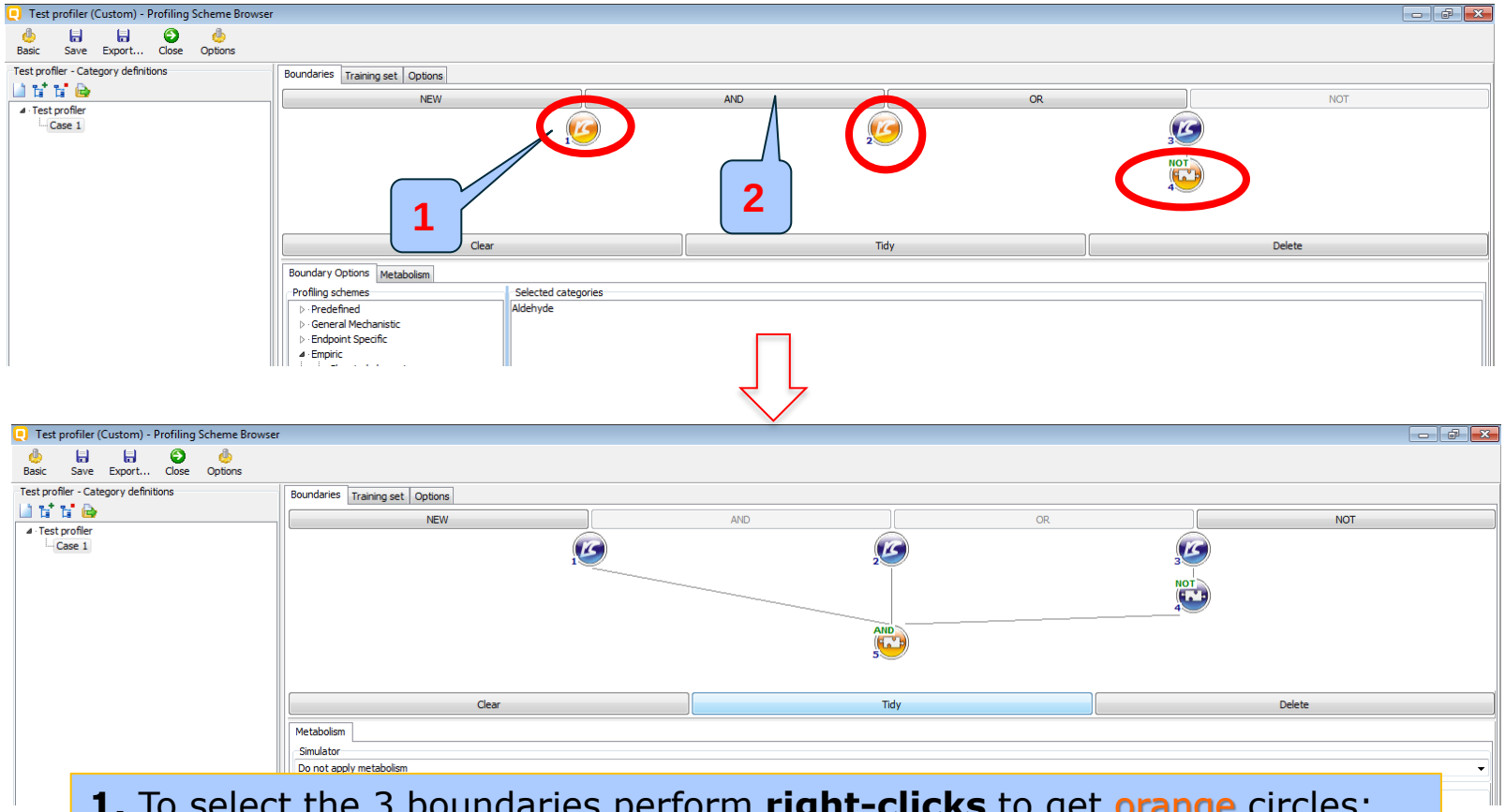
Building the category definition – rule 3



1. Create new referential boundary; **2. Select** Protein binding by OECD; **3. Select** Michael addition category; **4.** to negate the boundary **click** NOT.

Building of a new profiler

Grouping the referential boundaries.



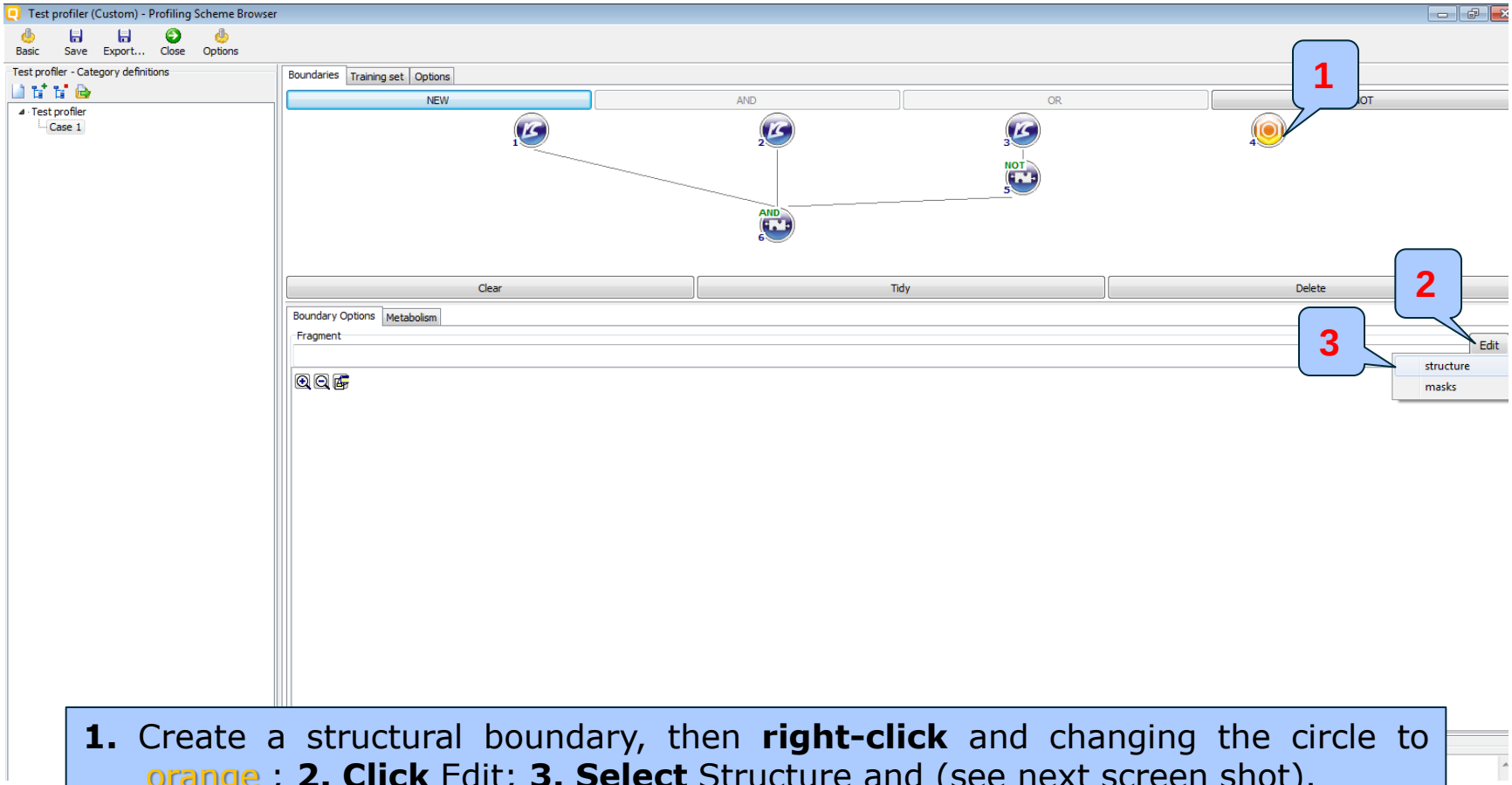
1. To select the 3 boundaries perform **right-clicks** to get orange circles;
2. Click AND.

Building of a new profiler
Restriction of the category definition

To complement the category definition add an instruction for ignoring those structures which have the fragment C(=O)(O)c1ccccc1 (where the aldehyde group is deactivated - no binding with protein) - rule 4.

Building of a new profiler

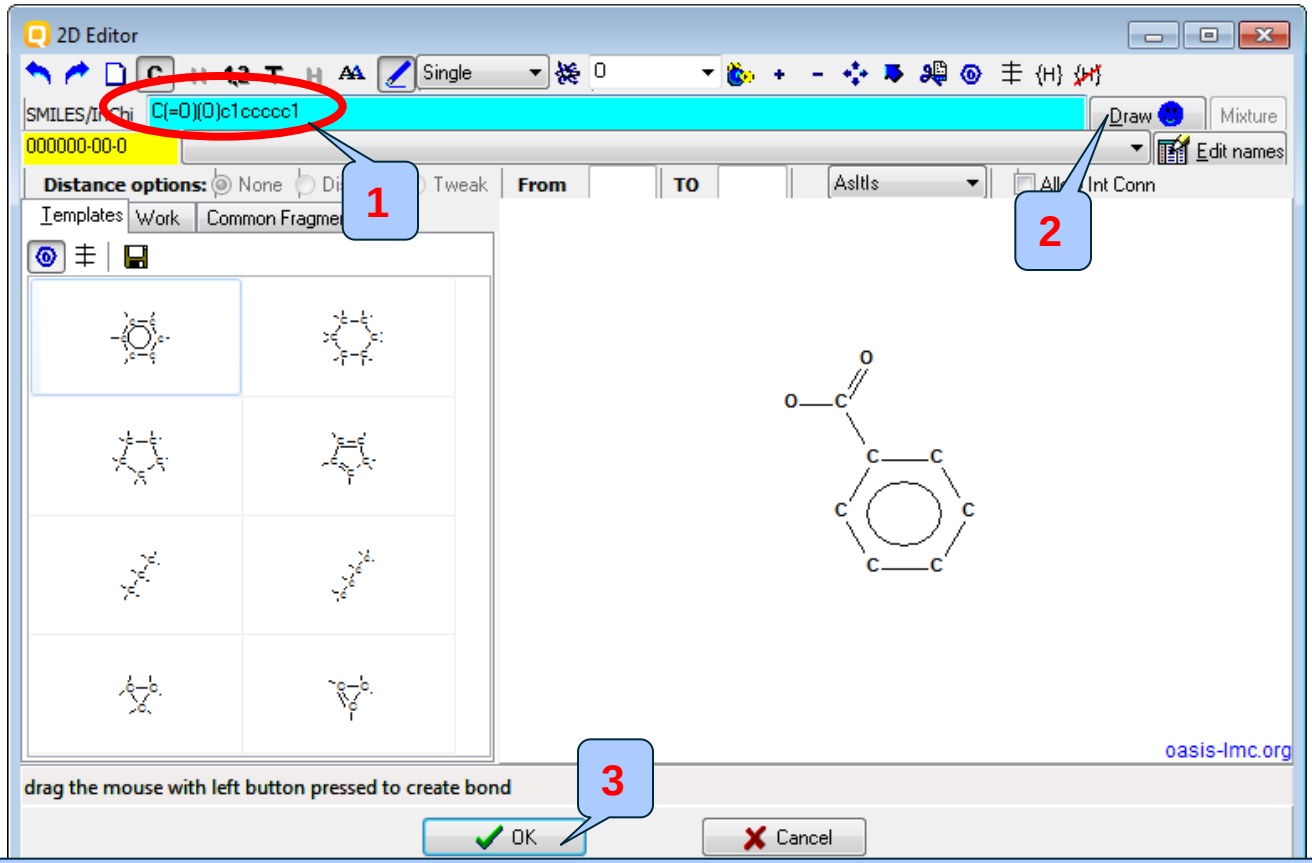
Building the category definition – rule 4



1. Create a structural boundary, then **right-click** and changing the circle to orange ; **2. Click** Edit; **3. Select** Structure and (see next screen shot).

Building of a new profiler

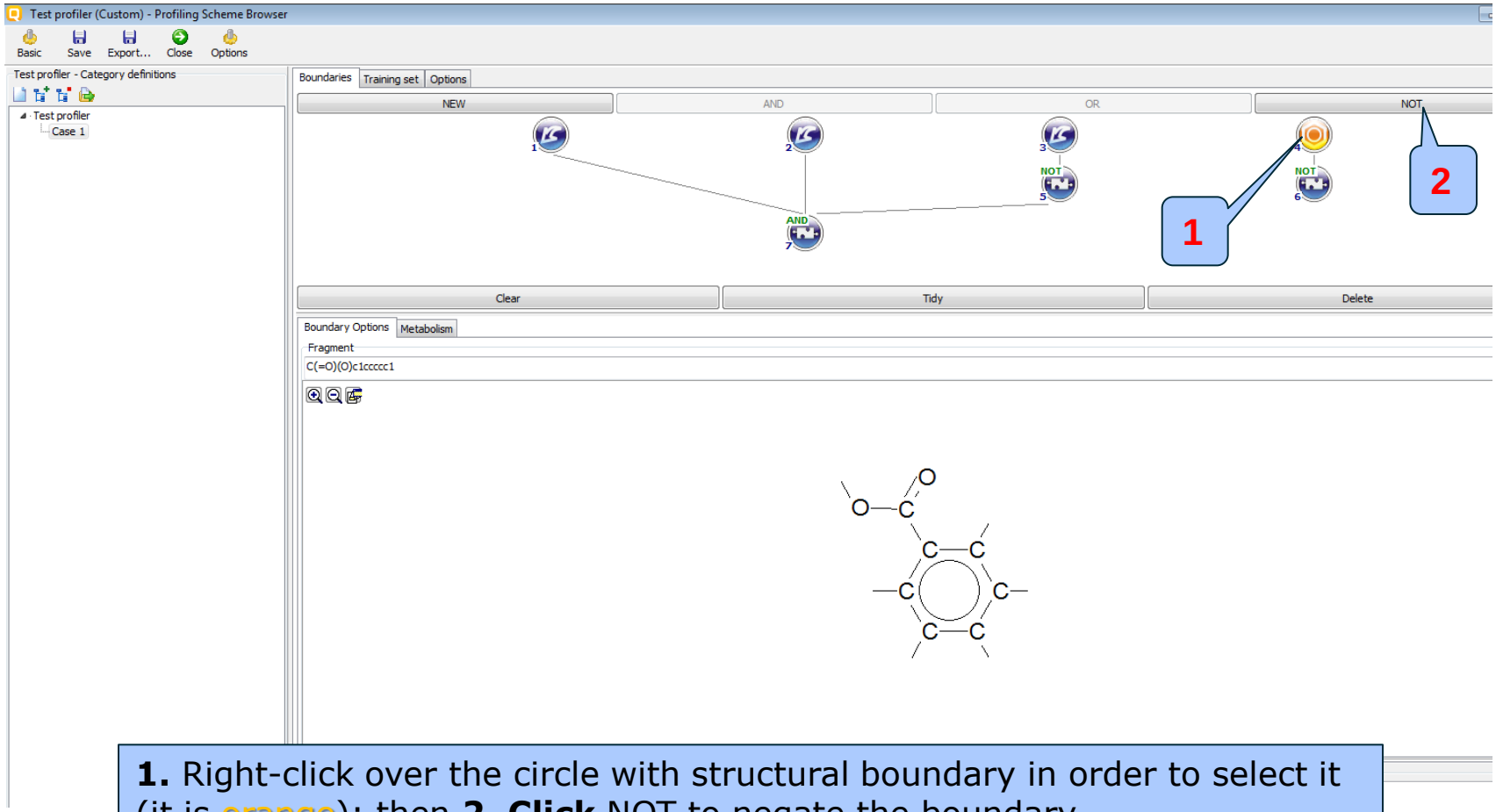
Building the category definition – rule 4



1. **Type** the SMILES of the fragment (or draw it in the 2D editor window);
2. **Click** Draw; **3. Click** OK.

Building of a new profiler

Building the category definition – rule 4



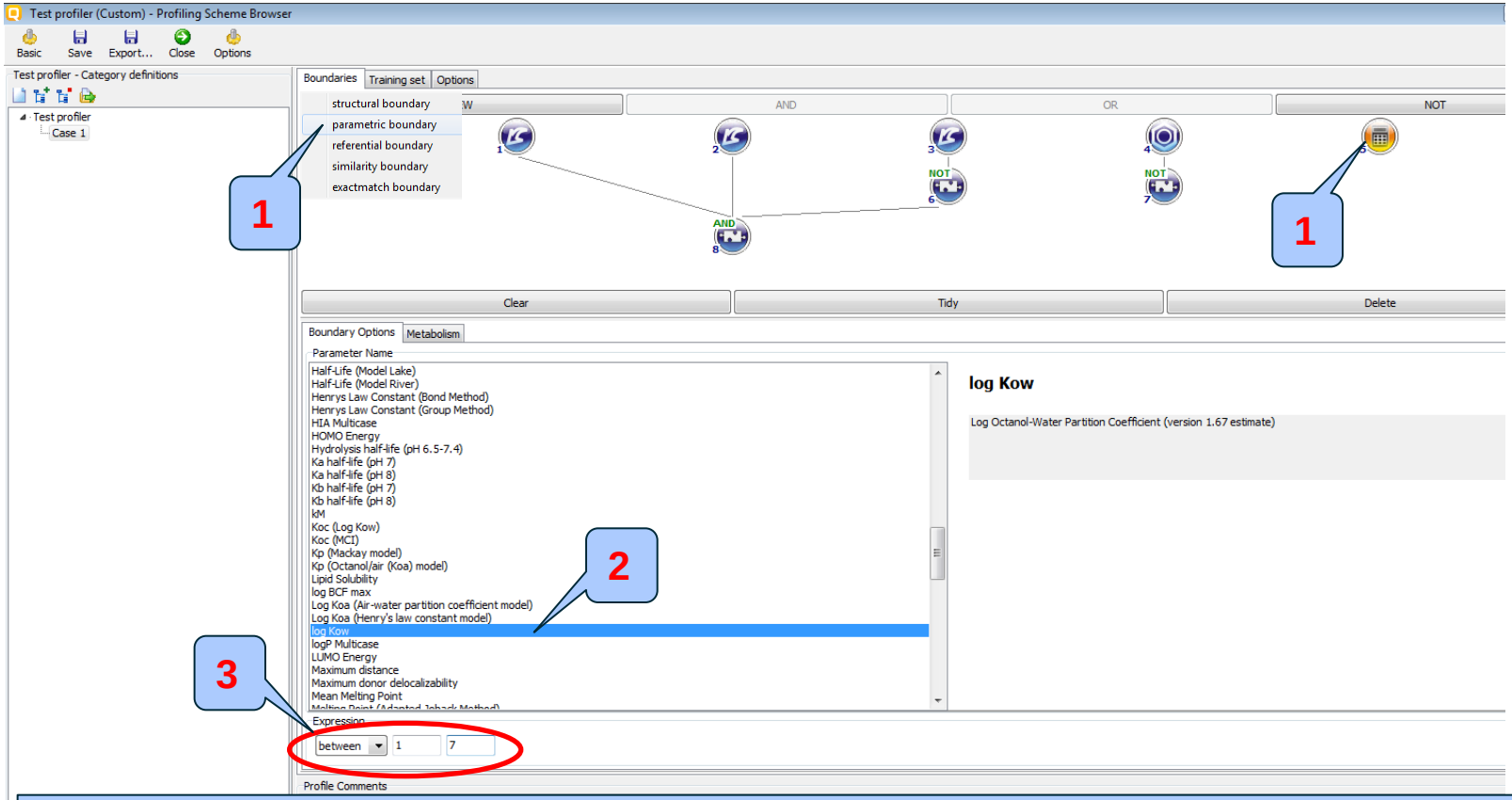
1. Right-click over the circle with structural boundary in order to select it (it is orange); then **2. Click** NOT to negate the boundary.

Building of a new profiler
Parametric range

To specify the needed parametric range, add a parametric boundary and combine it together with the rest boundaries in an AND query. The parametric range is log Kow between 1 and 7 (rule 5).

Building of a new profiler

Building the category definition – rule 5

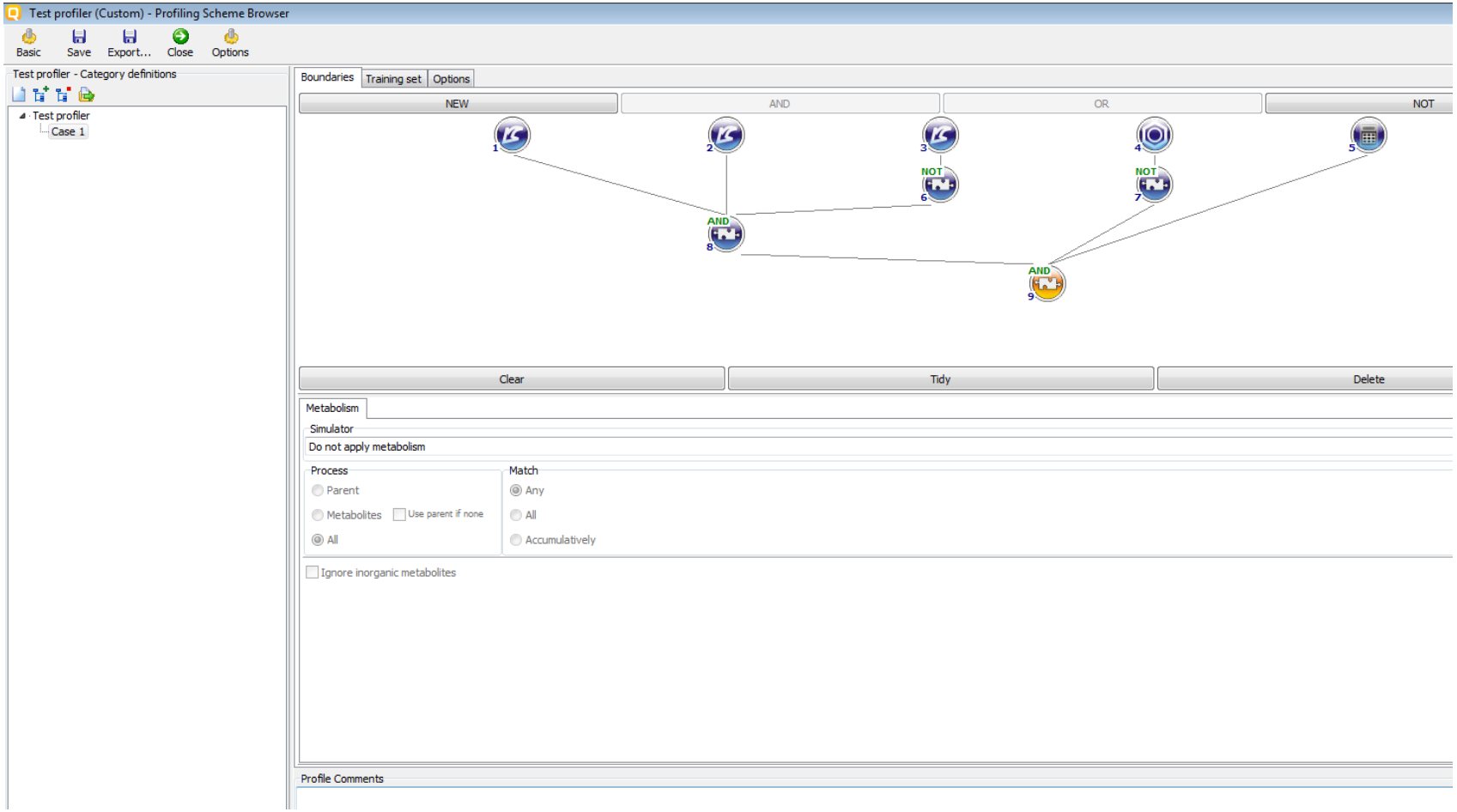


1. Create the parametric boundary and change the circle to orange; **2.** From the list with parameters **select** log Kow; **3. Select** qualifier between and enter the requisite values (1 to 7).

Building of a new profiler
Combine boundaries

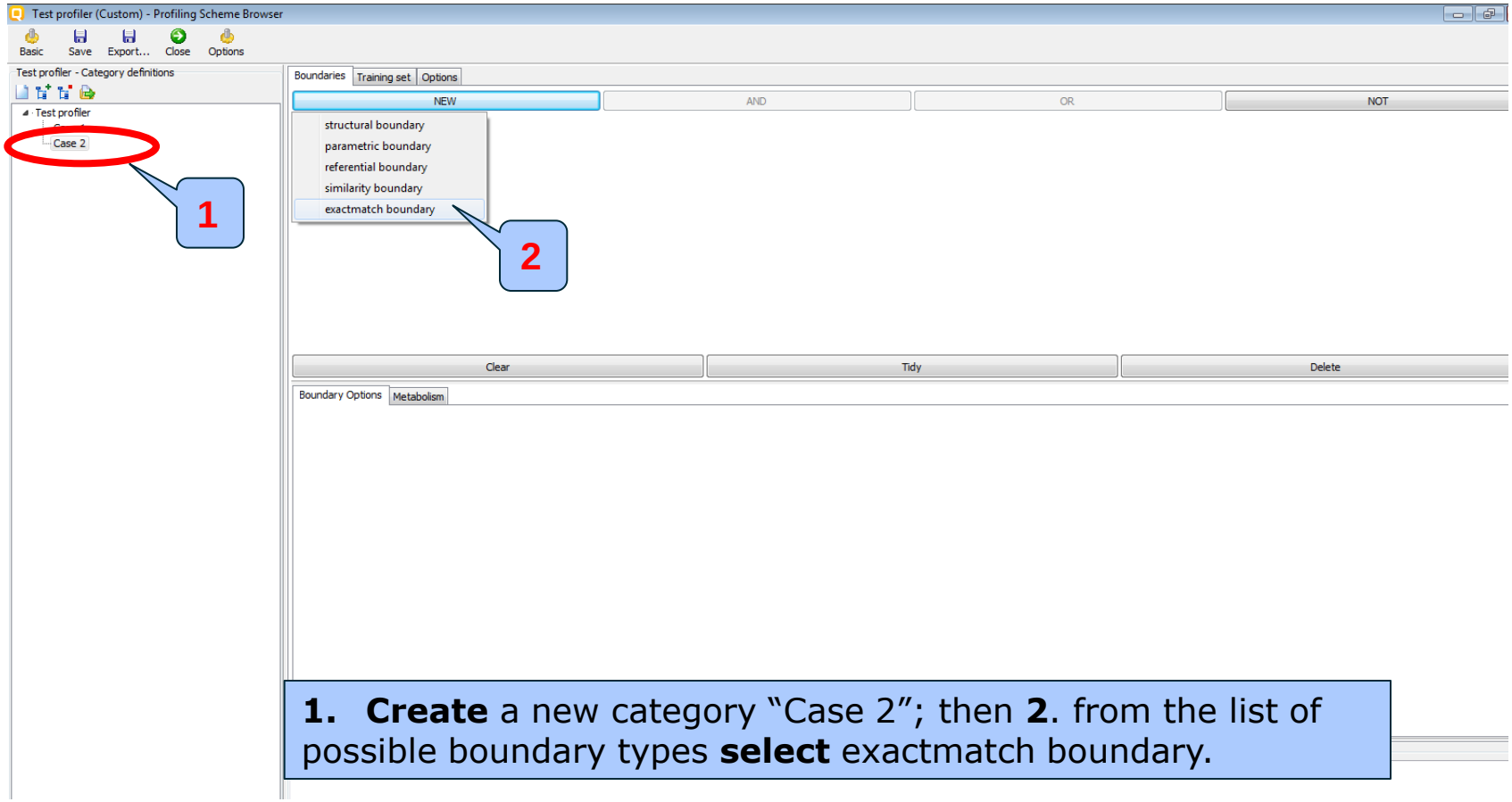
Finally, group the combined referential boundaries, the structural restriction and the parametric range in one single AND query.

Building of a new profiler
Combine boundaries



Building of a new profiler

Add a new category within the profiler

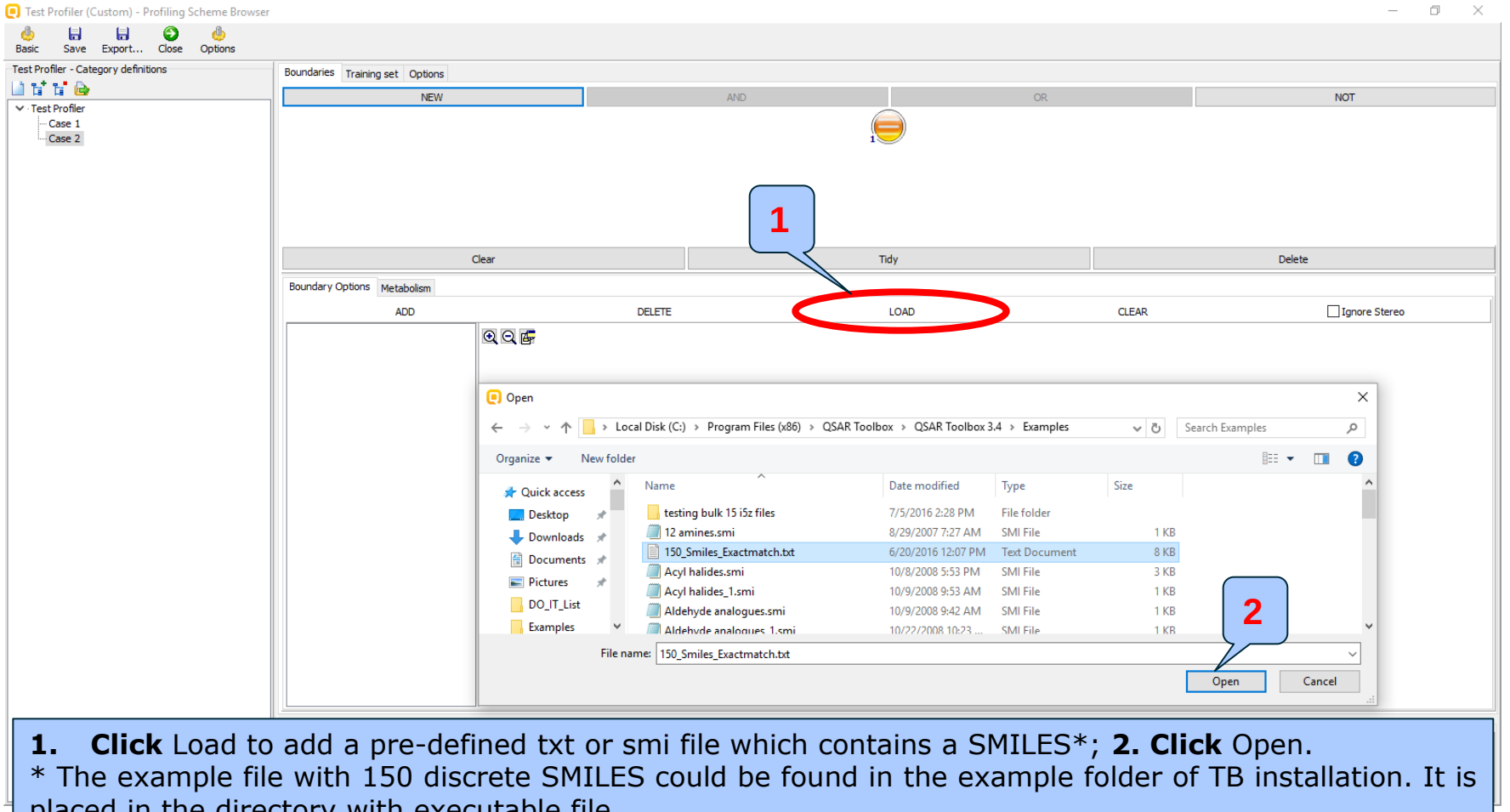


1. Create a new category "Case 2"; then **2.** from the list of possible boundary types **select** exactmatch boundary.

Building of a new profiler
Exactmatch boundary

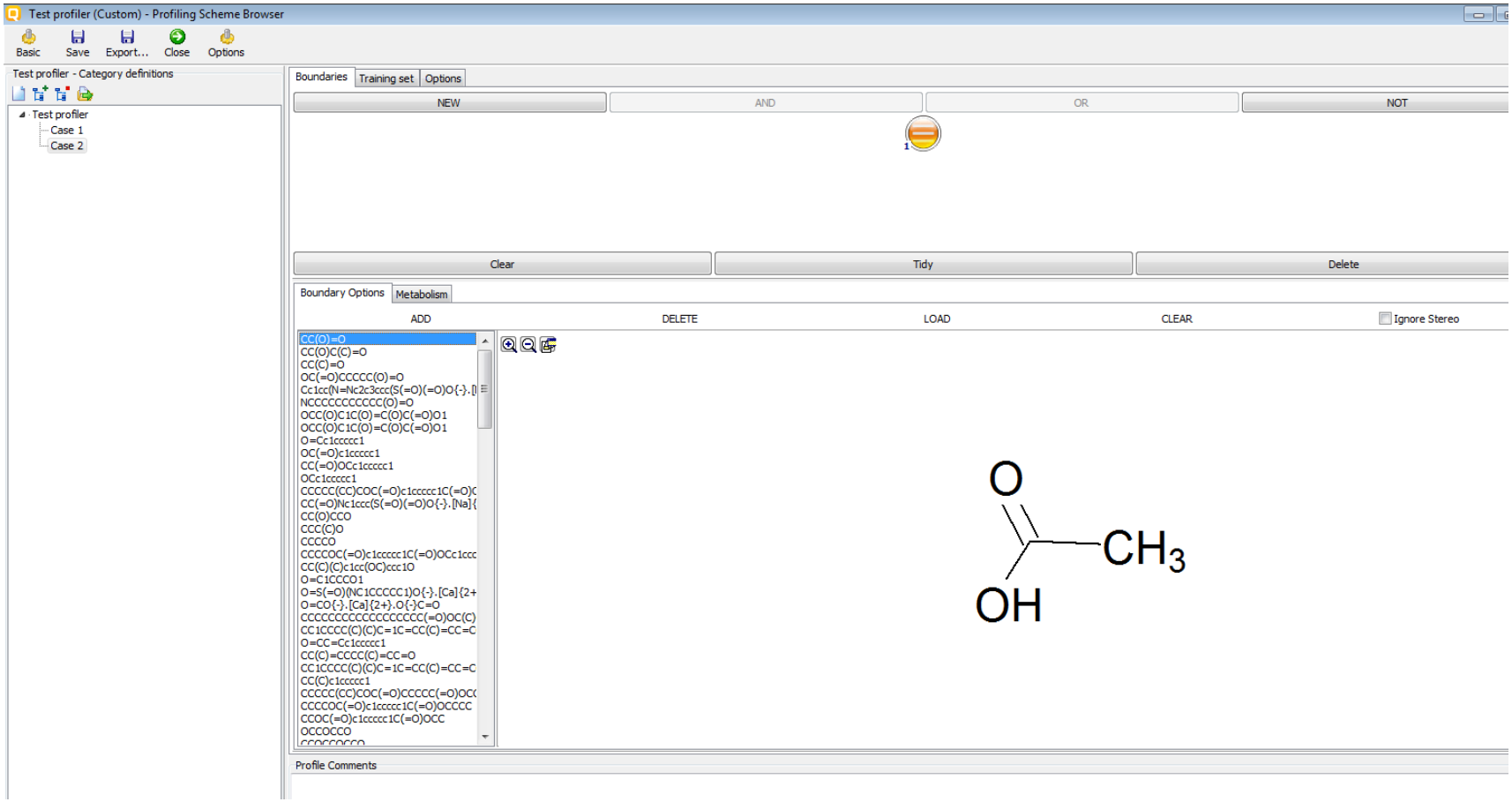
- The exact match boundary presents search by list of structures (SMILES). If the target chemical belongs to the loaded in boundary list, it fulfills the category definition.
- It is possible to logically combine the exactmatch boundary with boundaries of different type.

Building of a new profiler
exactmatch boundary



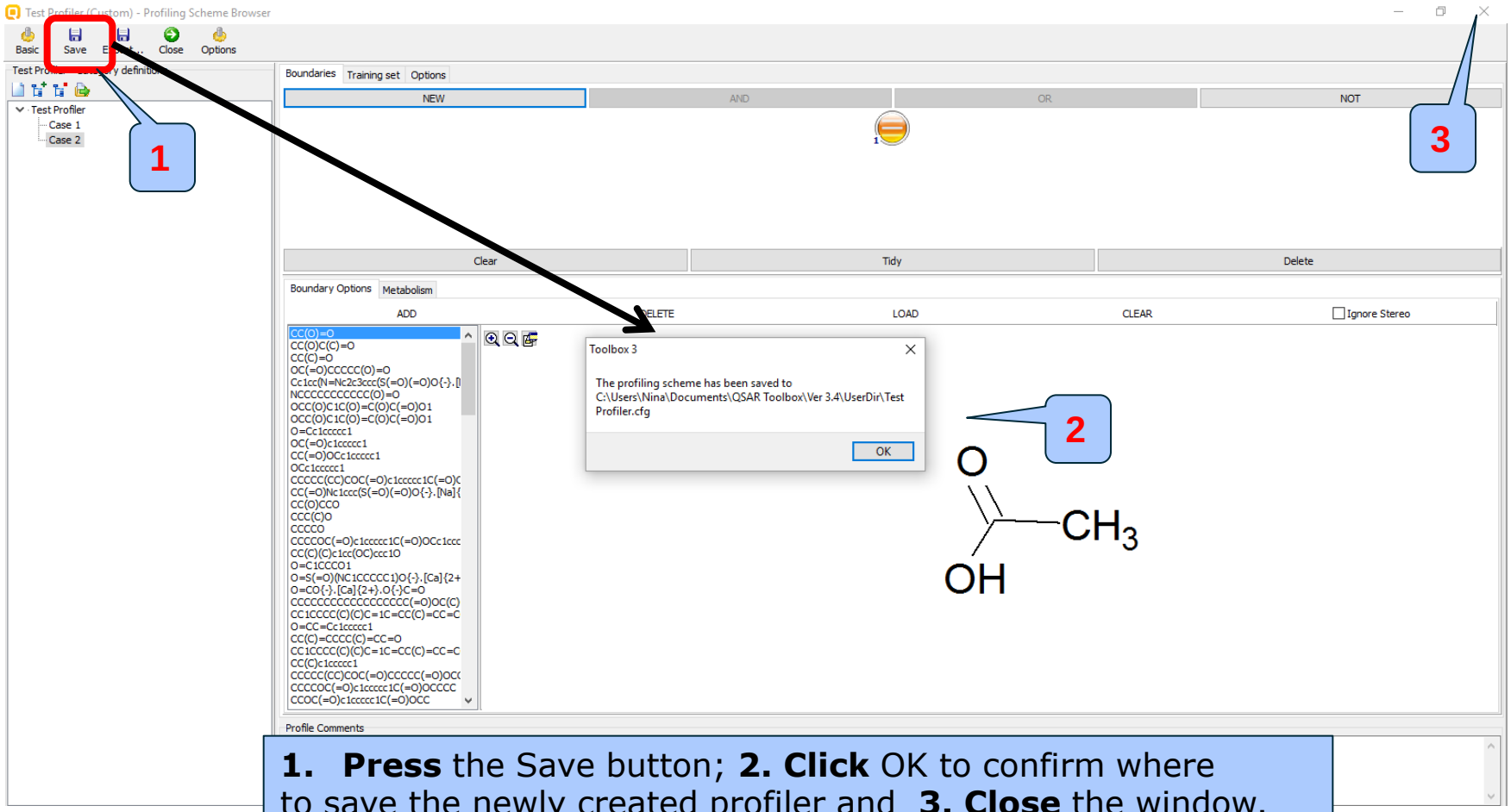
1. Click Load to add a pre-defined txt or smi file which contains a SMILES*; **2. Click** Open.
* The example file with 150 discrete SMILES could be found in the example folder of TB installation. It is placed in the directory with executable file.

Building of a new profiler
exactmatch boundary



Building of a new profiler

Final step – save the profiler

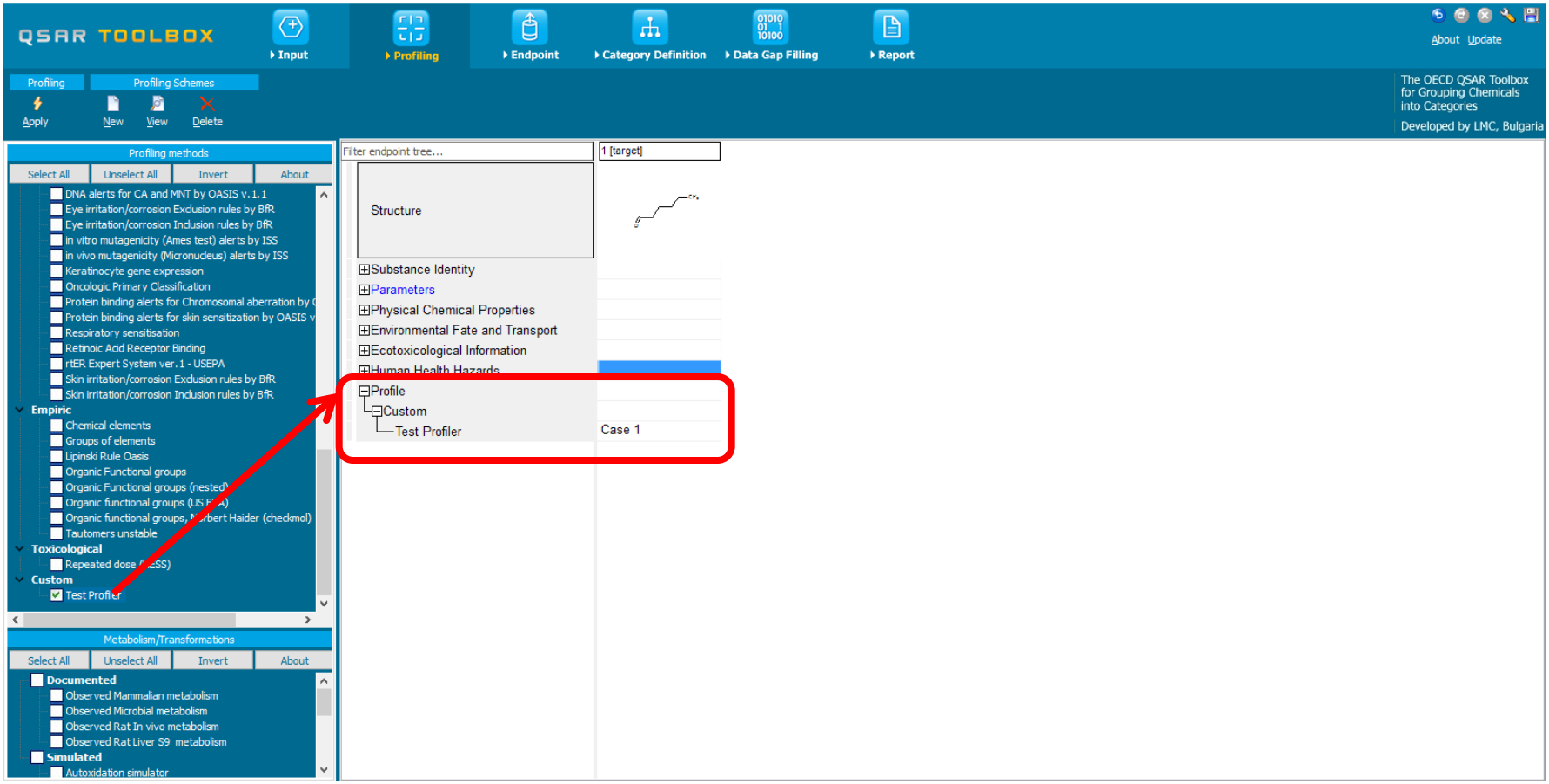


1. Press the Save button; **2. Click** OK to confirm where to save the newly created profiler and **3. Close** the window.

New profiler

The new profiler can now be applied to a target chemical or a list of chemicals complying with the newly constructed category definitions (see next screen shot).

New profiler
Results



Congratulation

- You have used several new functions to create a new profiler for use with the Toolbox.
- Continual use of the Toolbox will increase your skills.