QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

OECD (Q)SAR Toolbox v.4.4.1

Tutorial on how to predict skin sensitisation potential by standardized workflow

Outlook

- **Background**
- Keywords
- Objectives
- Specific Aims
- Standardized workflow for Skin sensitization
- The exercise
- Standardized workflow execution

Background

- This is a step-by-step presentation designed to take the Toolbox user through the filling of skin sensitization data gaps using a standardized workflow.

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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 the Toolbox:

- Identify analogues for a target chemical;
- Retrieve experimental results available for those analogues;
- Color the profiling schemes according to their suitability for subcategorization;
- Fill data gaps by standardized workflow;

Outlook

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Specific Aims

- To introduce to the Toolbox user to the standard workflow for predicting of skin sensitization potential;
- To familiarize the user with the new Toolbox interface;
- To familiarize the user with the new notification messages;
- To explain to the user the rationale behind each step of the exercise.

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- **Standardized workflow for Skin sensitization**
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Standardized workflow for Skin sensitization

Overview

- The standardized workflow (SW) is designed to apply data gap filling for discrete chemicals only
- The SWs has been developed to be applicable for the same endpoints used for application of the AWs (i.e. Skin sensitization, in vivo, LLNA and GPMT).
- Once started, the SW follows the implemented logic under the user control.
- As opposite to the automated workflow (AW), the domain of application is expanded in the SWs (including other species, durations, etc.) and SWs allow interactions by the user.
- In case more than one further application is possible, the workflow stops and waits for the decision of the user.
- SW can be executed for a single chemical only.

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The Exercise

- In this exercise we will predict the skin sensitization potential of Ethylparaben [CAS# 120-47-8], which will be the "target" chemical.
- This prediction will be accomplished by using of the developed standardized workflow for skin sensitization.

The Exercise
Background On Sensitization

- Allergic contact dermatitis that results from skin sensitization is a significant health concern.
- Skin sensitization is a toxicological endpoint that is complex and conceptually difficult.
- Many organic chemicals have been shown to induce skin sensitization after covalent binding to skin proteins[1].
- Therefore, mechanisms by which organic chemicals bind with proteins are relevant to grouping chemicals that may be skin sensitizing agents.

[1] OECD (2014), *The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins*, OECD Series on Testing and Assessment, No. 168, OECD Publishing, Paris, https://doi.org/10.1787/9789264221444-en.

Outlook

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Standardized workflow execution

- Only three of the general Toolbox modules are used in a sequential workflow:
  - Input
  - Data Gap Filling
  - Report

The rest of the modules – *Profiling*, *Data* and *Category definition* are included as a part of the algorithm of the standardized workflow. The workflow stops at them and waits for the decision of the user.

Outlook

- Background
- Keywords
- Objectives
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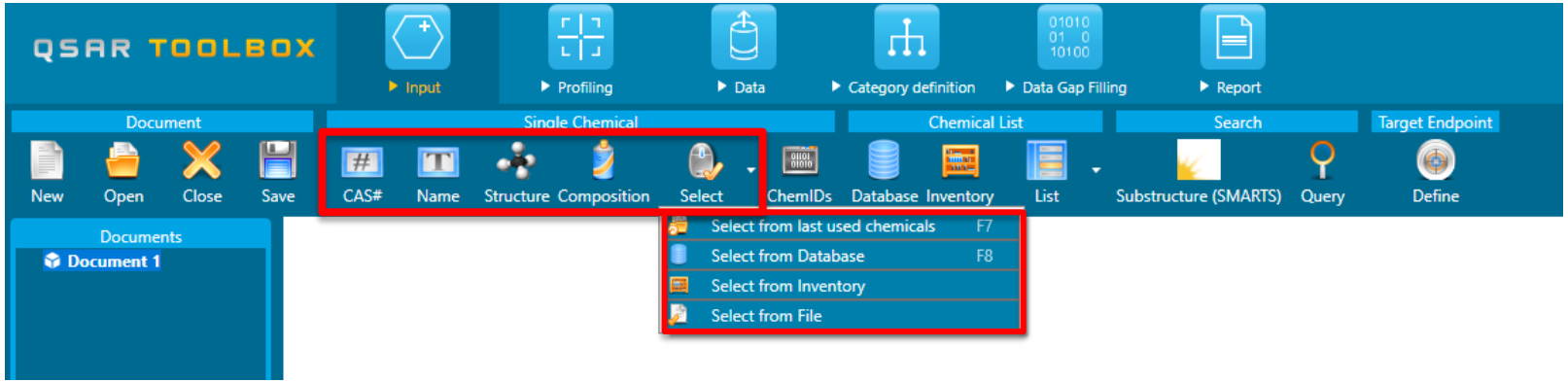
- Standardized workflow for Skin sensitization
- The exercise
- **Standardized workflow execution**
  - Input

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

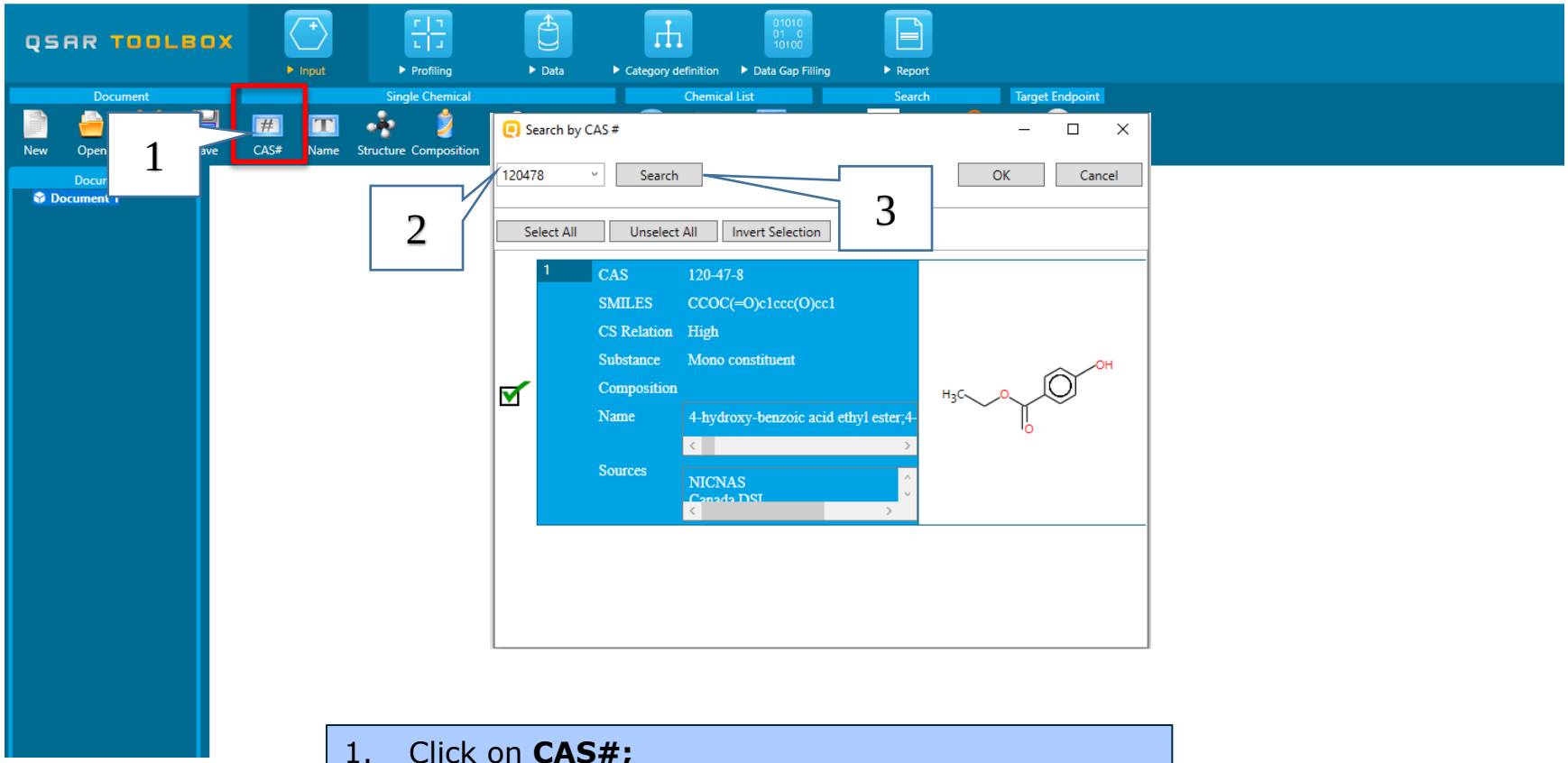
Ways of Entering a Chemical



- Chemical Name
- Chemical Abstract Services (CAS) number (#)
- Drawing chemical structure
- Select from User List/Inventory/Databases

Input Screen

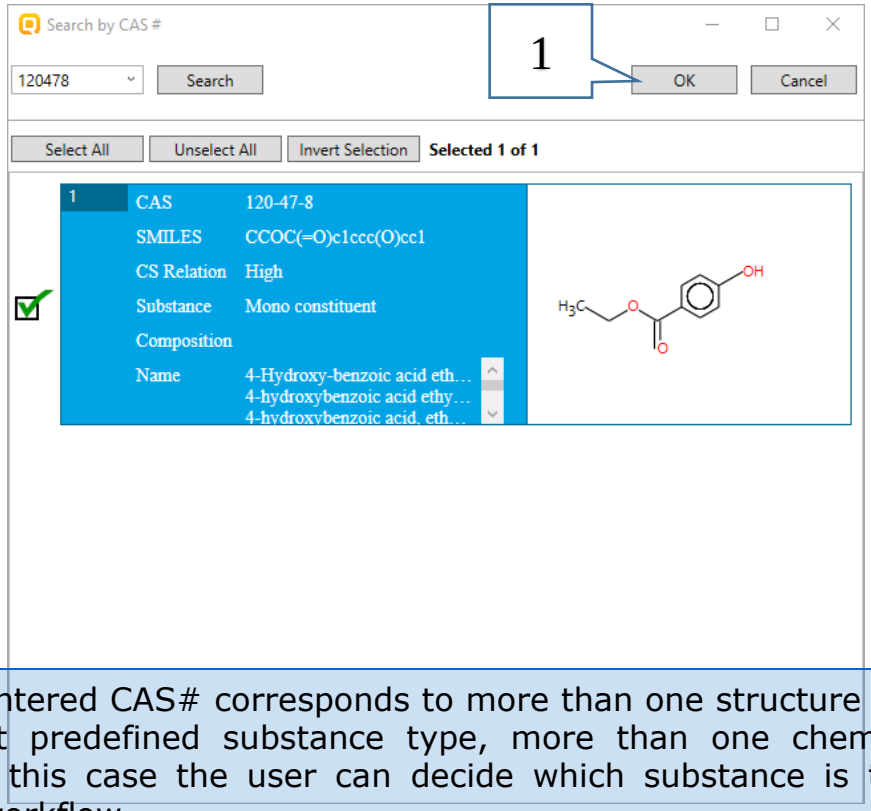
Input target chemical by CAS#



1. Click on **CAS#;**
2. Enter the CAS# of Ethylparaben (CAS **120-47-8**);
3. Click on **Search**.

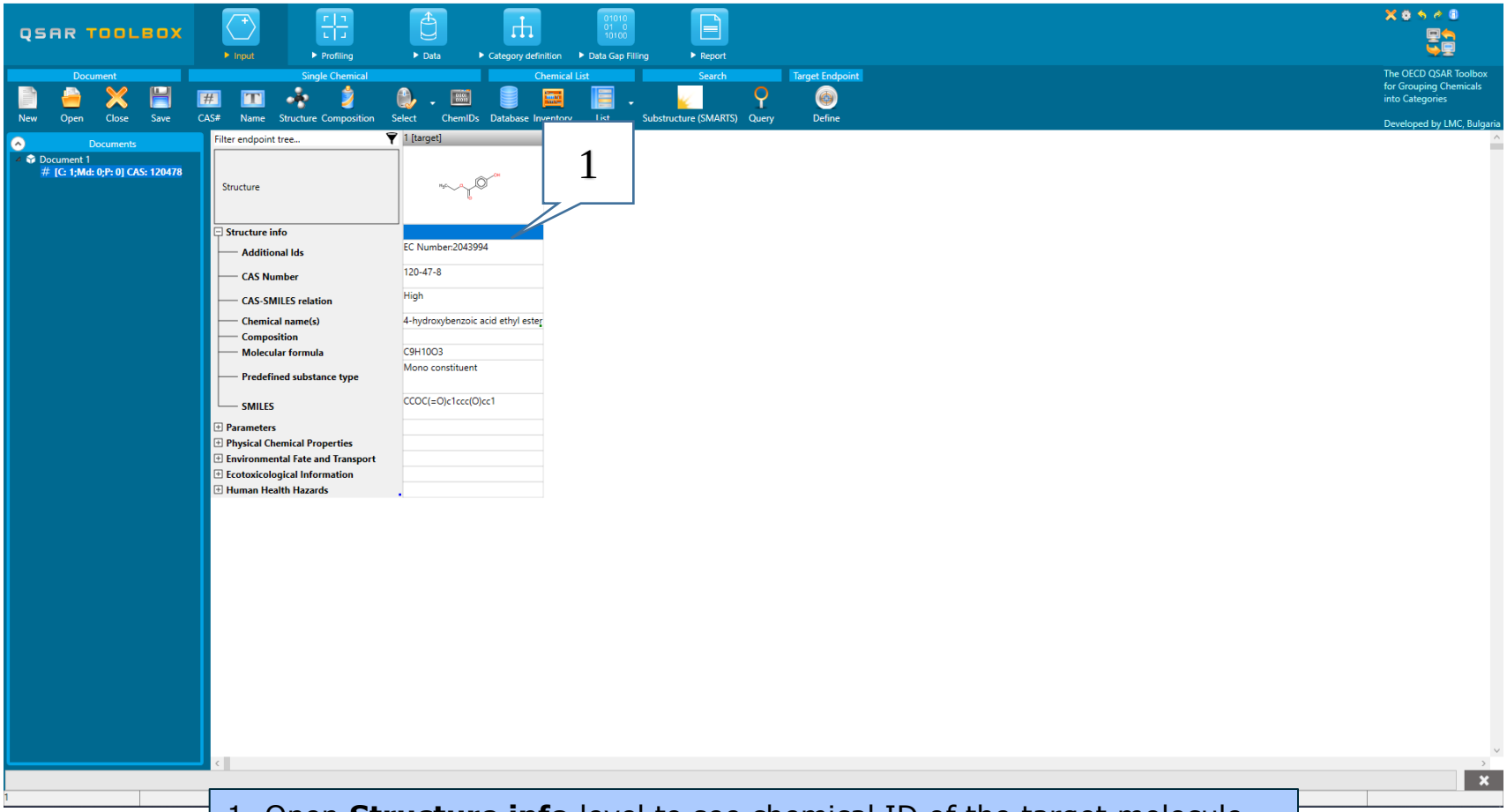
Input
Target chemical identity

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. Click on **OK** (1).



In case the entered CAS# corresponds to more than one structure or to one structure but with different predefined substance type, more than one chemical identity could be retrieved. In this case the user can decide which substance is to be retained for the subsequent workflow.

Input
Target chemical identity



1. Open **Structure info** level to see chemical ID of the target molecule

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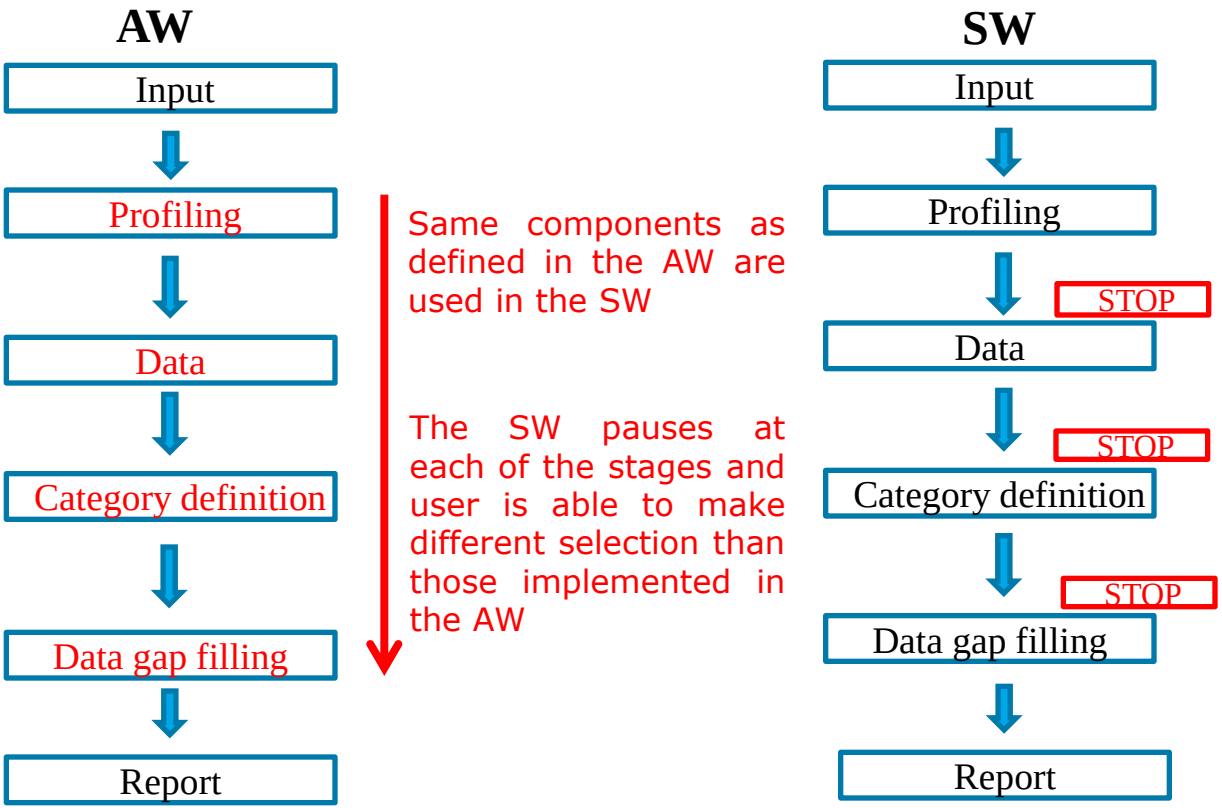
  - Input
  - **Data Gap Filling**

Data Gap Filling
Overview

- "Data Gap Filling" (DGF) module give access to five different data gap filling tools:
  - Read-across
  - Trend analysis
  - (Q)SAR models
  - Standardized workflow
  - Automated workflow
- 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.
  - Standardized and Automated workflows are developed to facilitate the users work. Once started, they follow the implemented logic and finish with prediction. The general differences between the two types of workflows are represented on the next slide.

Data Gap Filling
Overview



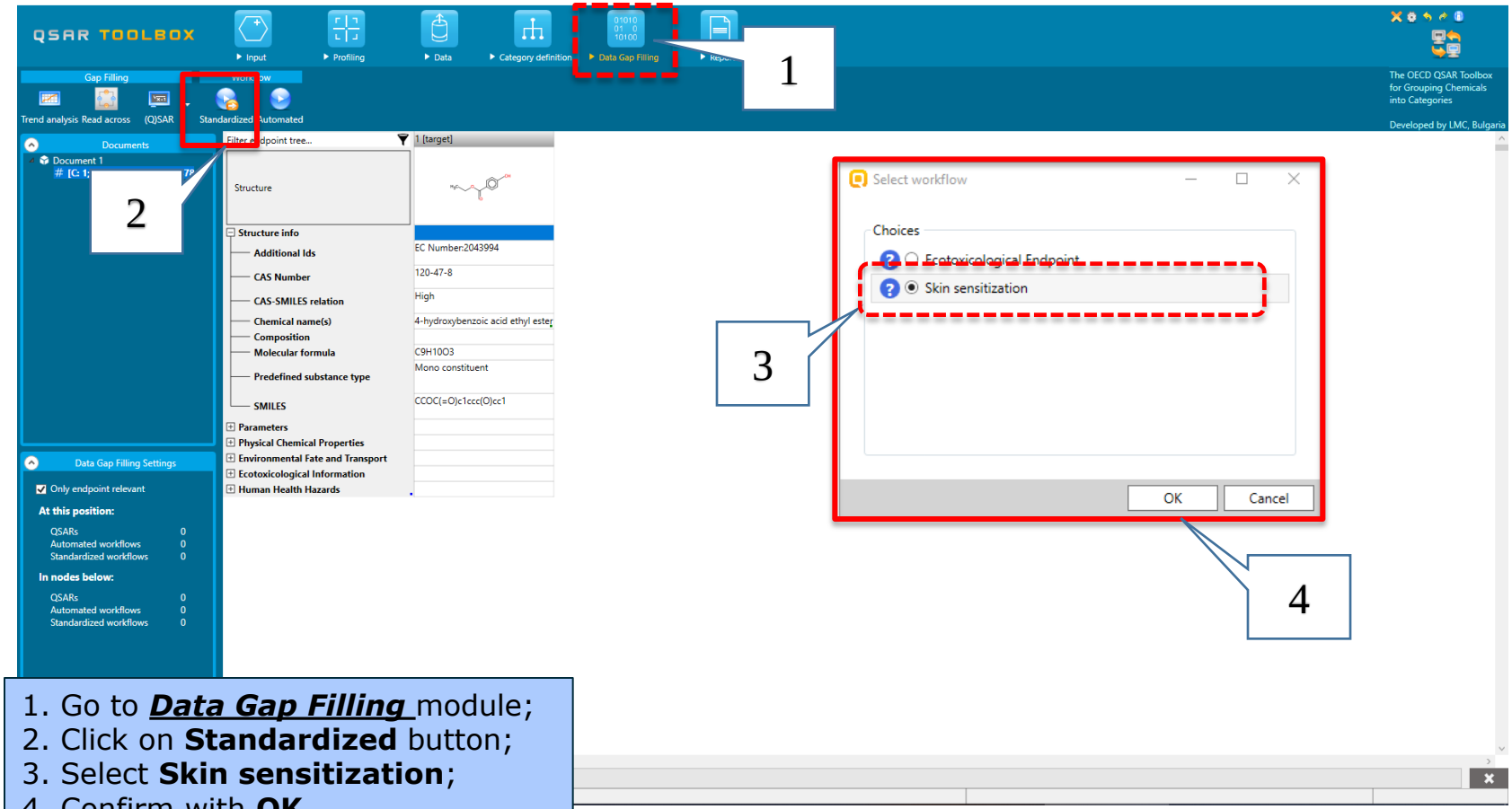
Databases with data for the target endpoint are listed and user select to use all of them or make specific selection.

Relevant to the workflow profilers appropriate for DGF are listed and ordered hierarchically based on the population of the group and user is able to select any of them.

Additional data filtering could be applied (e.g. different species selection)

In this example, we will use the Standardized workflow approach.

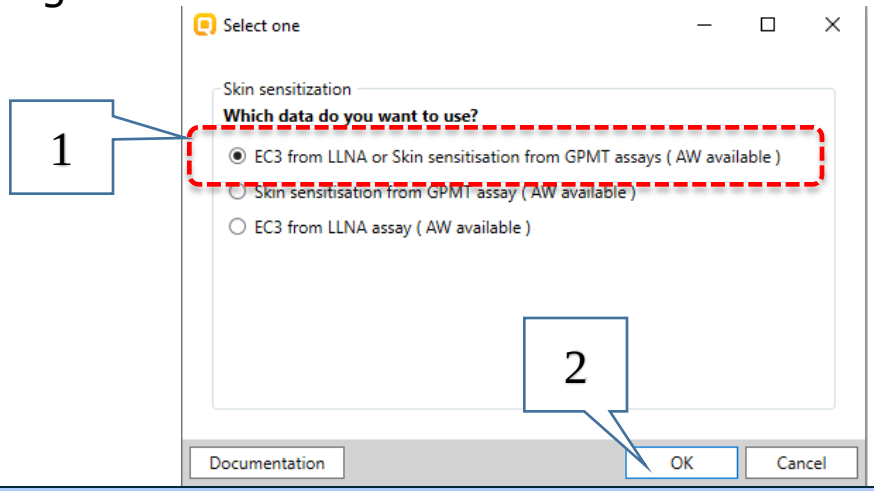
Data Gap Filling
Apply Standardized workflow



1. Go to ***Data Gap Filling*** module;
2. Click on **Standardized** button;
3. Select **Skin sensitization**;
4. Confirm with **OK**

Data Gap Filling
Apply Standardized workflow

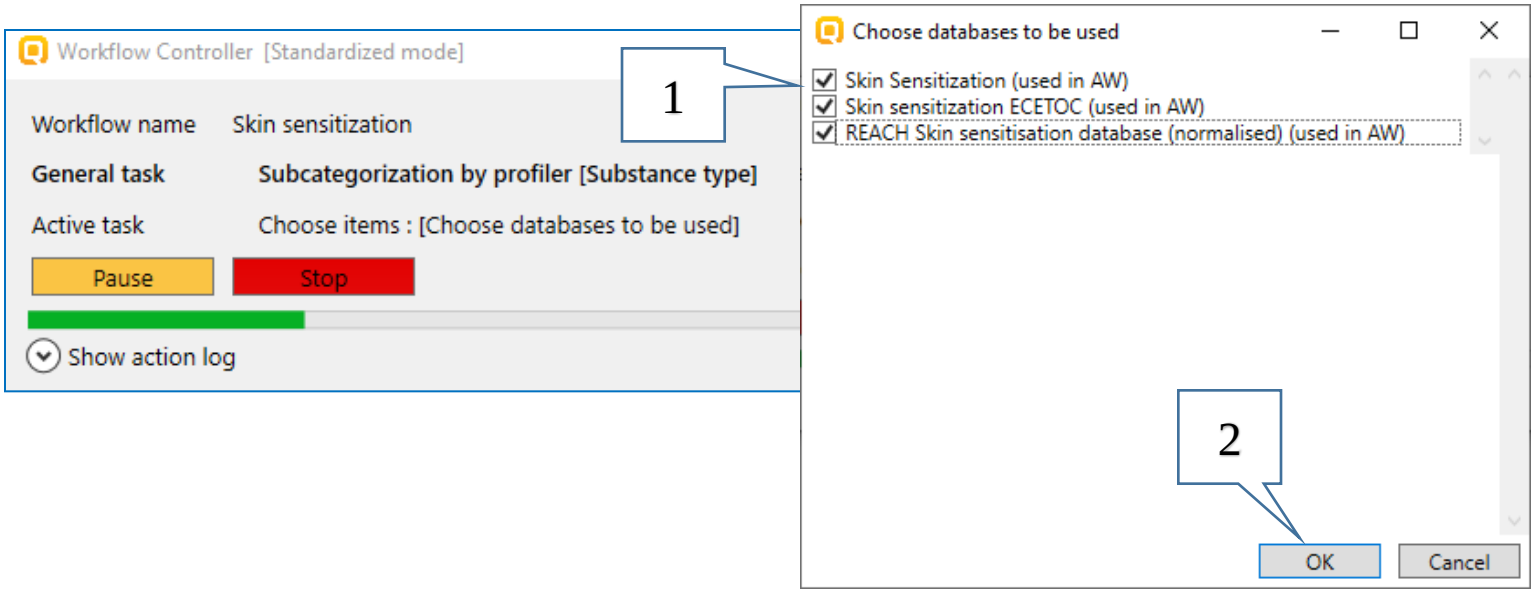
There are three options for selection of endpoint and the user should select one of them. The first option allows more analogues to be found because of using of two types of data – EC3 and SMWN. During the workflow process all skin data of these endpoints will be converted to the default scale for Skin Sensitisation - "Skin Sensitisation ECETOC". It converts all skin data into: Positive and Negative.



1. Select the first combined endpoint – **EC3 from LLNA and SMWN from GPMT assays**;
2. Confirm with **OK**

Data Gap Filling
Apply Standardized workflow

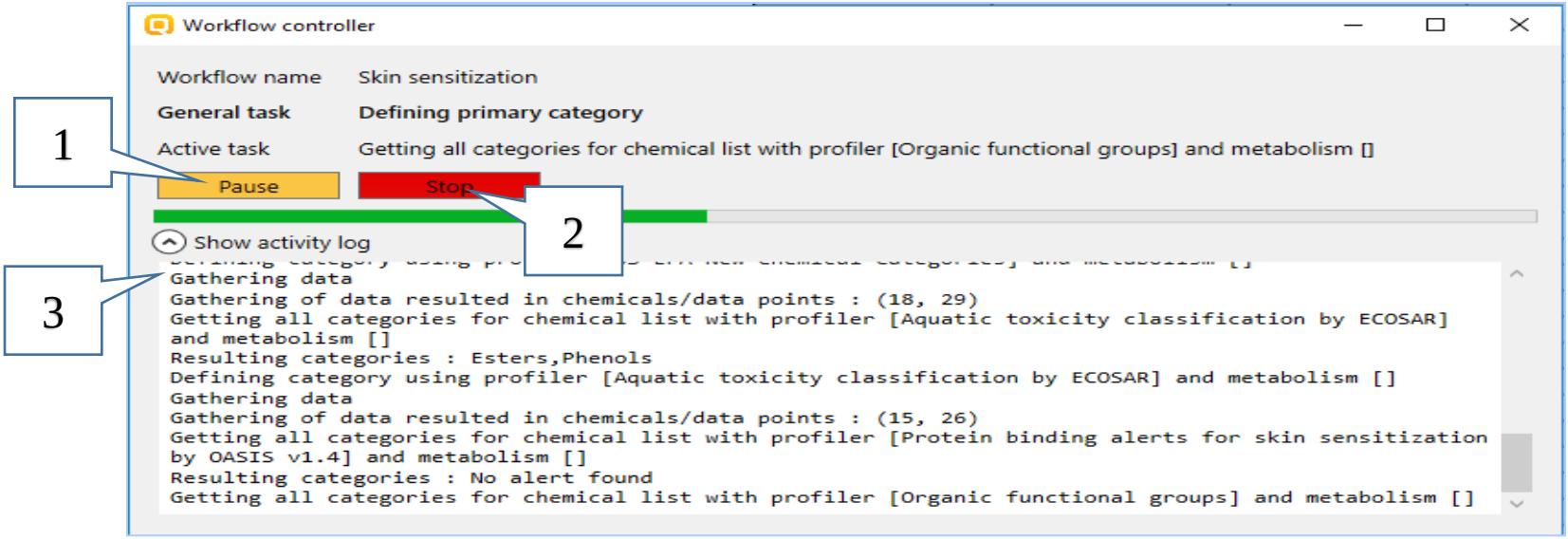
Once the workflow is started, *Workflow controller* appears. The first choice, which the user will have to make is to select one or all skin sensitization databases, where the analogues will be searched.



1. Select all databases – **Skin Sensitization, Skin sensitization ECETOC and REACH Skin sensitisation database (normalised)**;
2. Click on **OK**

Data Gap Filling
Apply Standardized workflow

The **Workflow controller** has two main buttons **Continue/Pause** (1) allowing to continue or pause and **Stop** (2) – which will stop the workflow. Additionally, all actions that will be done during the execution of the workflow are tracked down and could be seen from the **Show activity log** part (3) of the Workflow controller.



Data Gap Filling
Algorithm of Skin sensitization workflow

Once finished with the selection of databases, the workflow continues with application of the relevant profilers. There are three possible cases to form an analogues set:

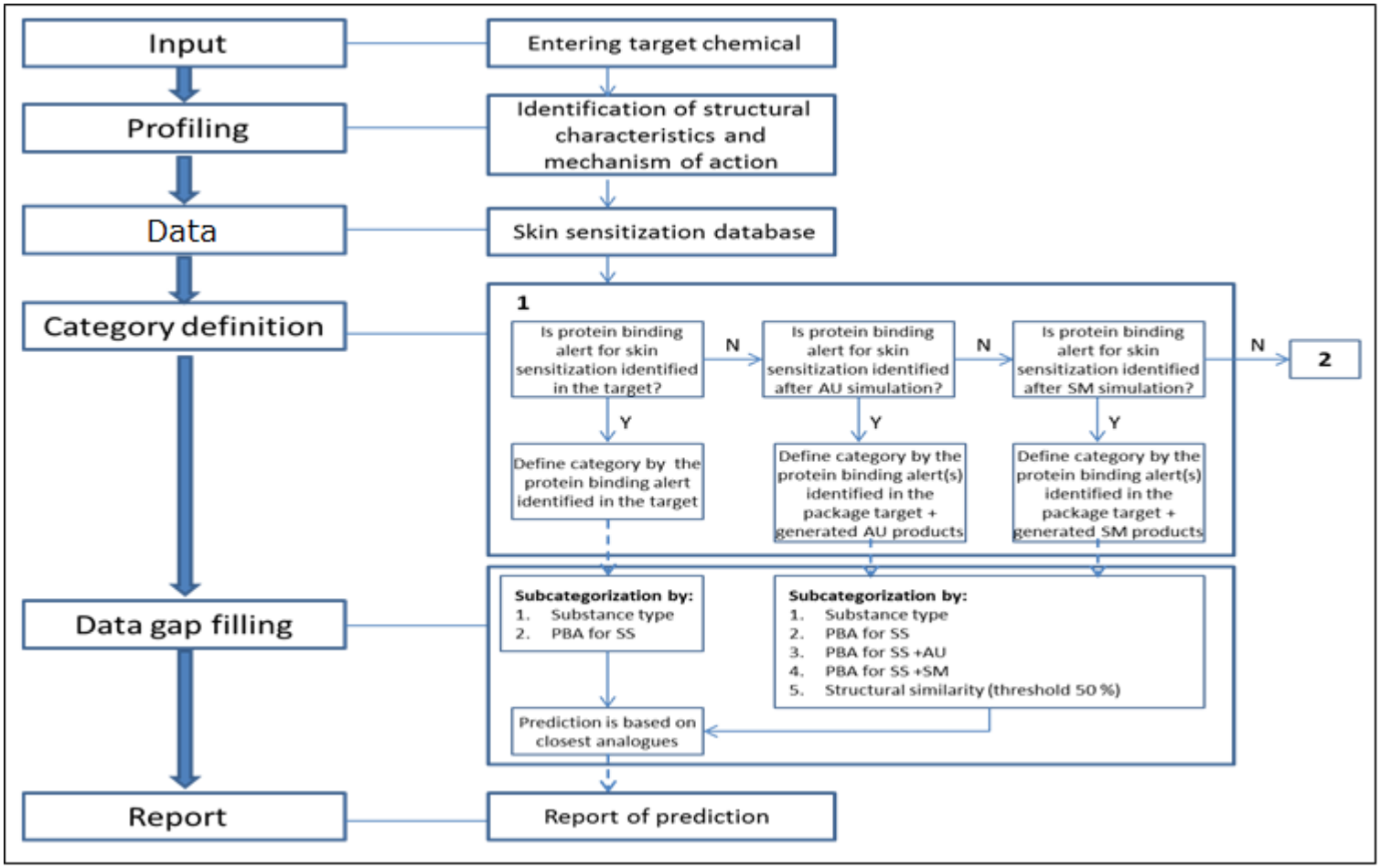
1) if the target has an active alert as a parent;
2) if the target has an active alert as a result of autoxidation or skin metabolism activation;
3) if no alert is found in the target or its metabolites.

If a protein binding alert is identified in the target or is produced as a result of autoxidation or skin metabolism (case 1 or 2) then primary grouping is based on this alert (scenario 1)
In the last case (case 3) the primary group is defined using structurally based profiling schemes (scenario 2).

Graphical representation of both scenarios are illustrated on next two slides.

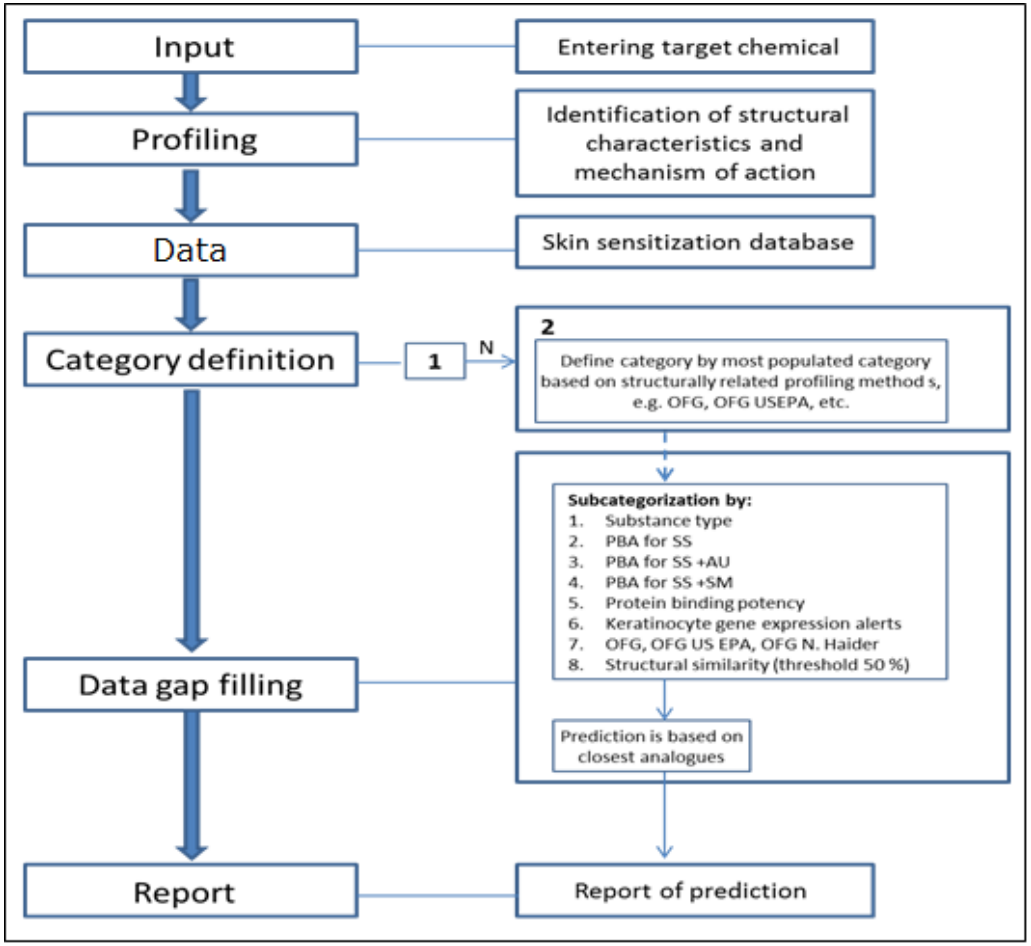
Data Gap Filling

Scenario 1 – an alert is identified in the parent or produced as a result of autoxidation or skin metabolism activation



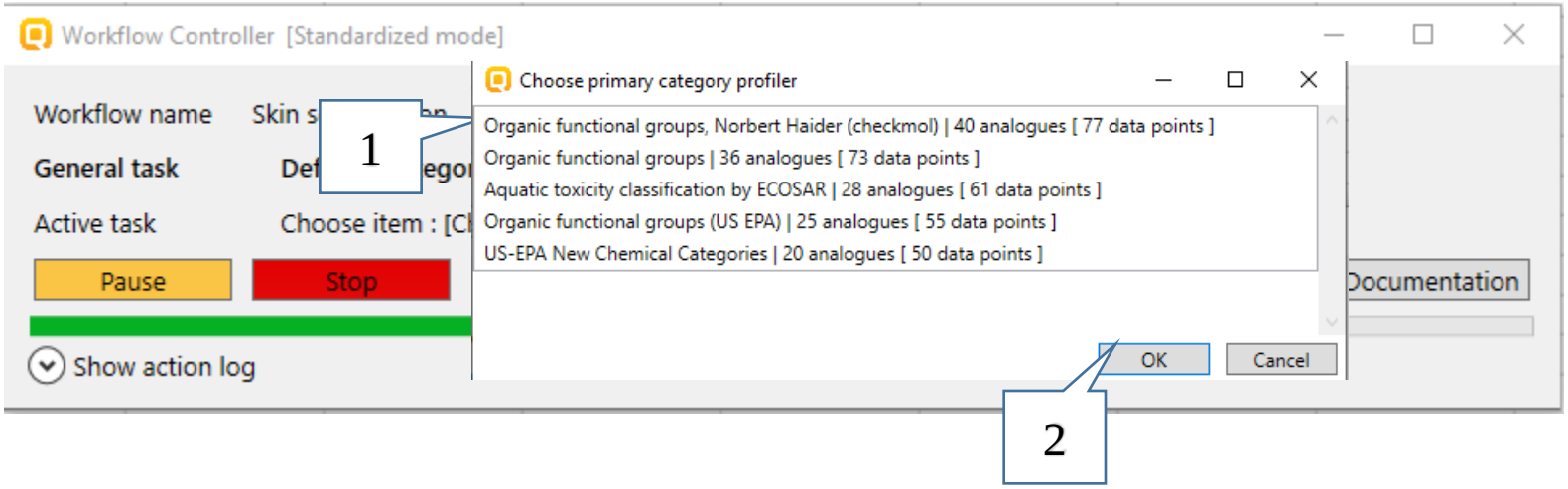
Data Gap Filling

Scenario 2 – no alert is identified in the parent neither in generated metabolites (autoxidation products and skin metabolites)



Data Gap Filling
Apply Standardized workflow

When a group cannot be defined by the workflow (more than one alert available in the target chemical or different primary groupings based on structure based profilers) then the standardized workflow waits for action from the user.



1. For example you could continue the workflow with the most populated category (by default listed as first in the list);
2. Confirm with **OK**

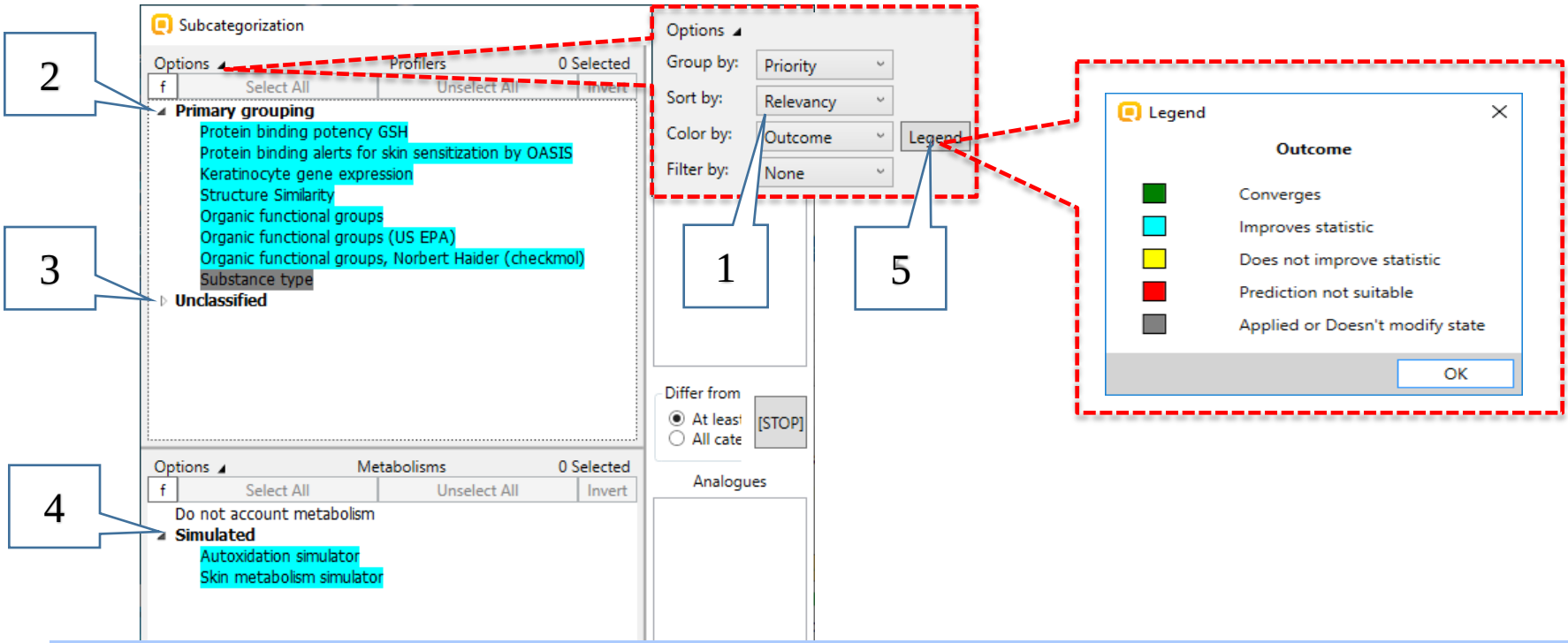
Data Gap Filling
Apply Standardized workflow

When the profiling scheme for primary categorization is selected, the workflow makes a category and enters in Data Gap Filling, where the next step is subcategorization. Depending on the outcome obtained by the applied subcategorization, the profilers are colored as follows:

- **Green** – application of the profiler will satisfy the criteria for acceptance of the prediction
- **Blue** – application of the profiler increase the confidence of the prediction only
- **Yellow** – application of the profiler does not change the current state
- **Red** – criteria for acceptance the subcategorization will be not reached
- **Grey** – already applied profiler

Data Gap Filling

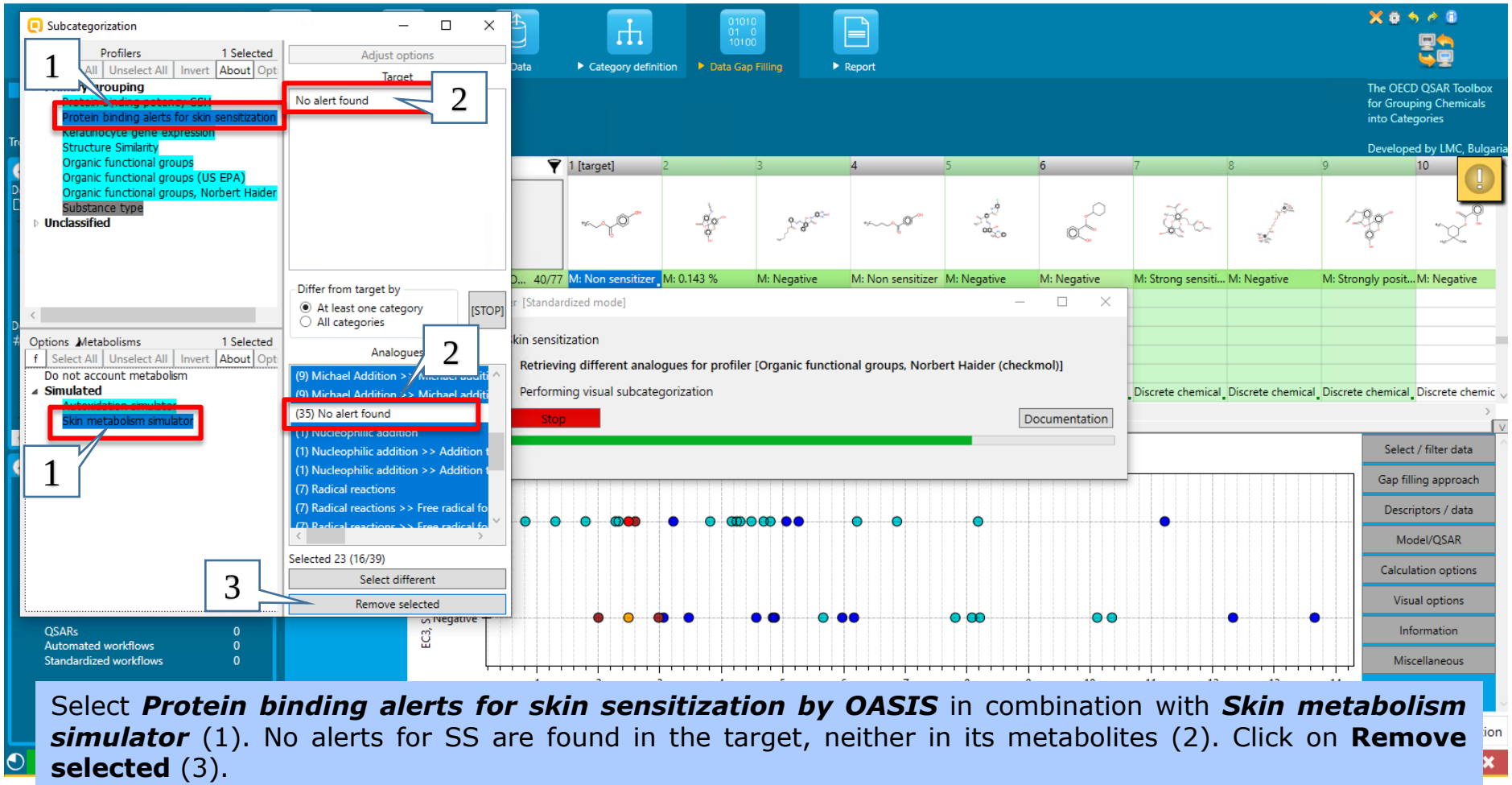
Apply Standardized workflow



The profilers are sorted by ***Relevancy*** (1) and the highlighted profilers appear in group ***Primary grouping*** (2). All the rest profilers are stored under group ***Unclassified*** (3). Although the highlighted profiles are relevant to the endpoint, recommended and facilitating the user in their further choice, the rest of the profilers are not removed and user can select each of them for subcategorization.
In case the target have no alerts as a parent, the related metabolic simulator will be also highlighted (4).
A legend of the colors is also available (5)

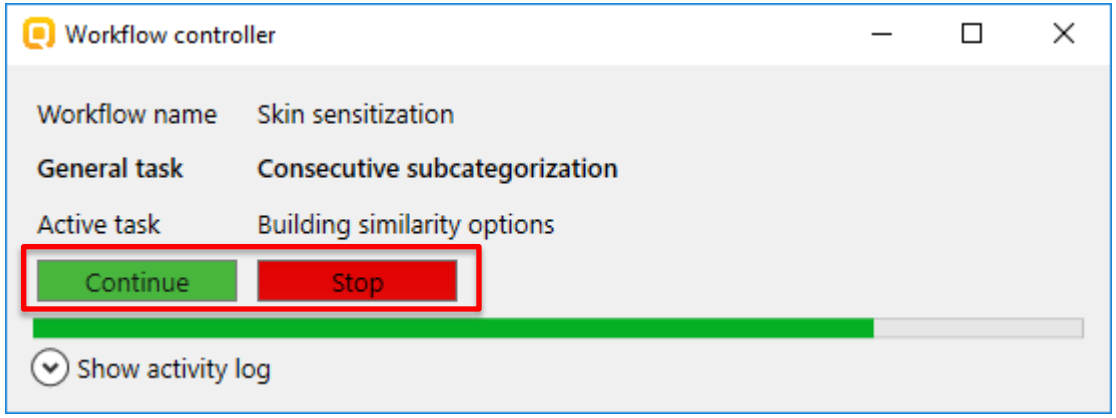
Data Gap Filling

Apply Standardized workflow



Select ***Protein binding alerts for skin sensitization by OASIS*** in combination with ***Skin metabolism simulator*** (1). No alerts for SS are found in the target, neither in its metabolites (2). Click on **Remove selected** (3).

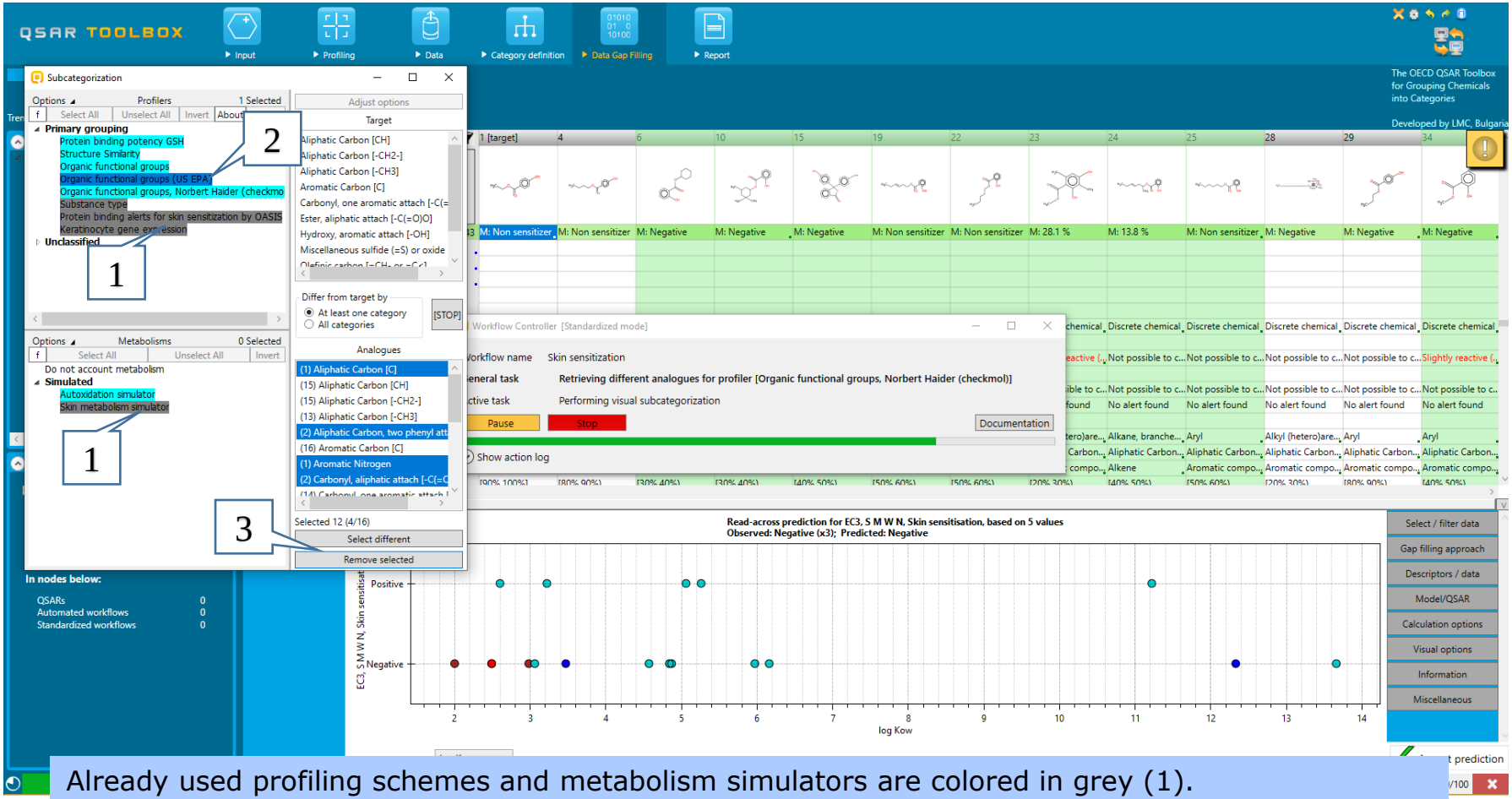
Data Gap Filling
Apply Standardized workflow



When the chemicals, which fulfill the requirements are removed, the *Workflow controller* stops before the next subcategorization. The user can continue to subcategorize or to stop, accepting the current state of the prediction.

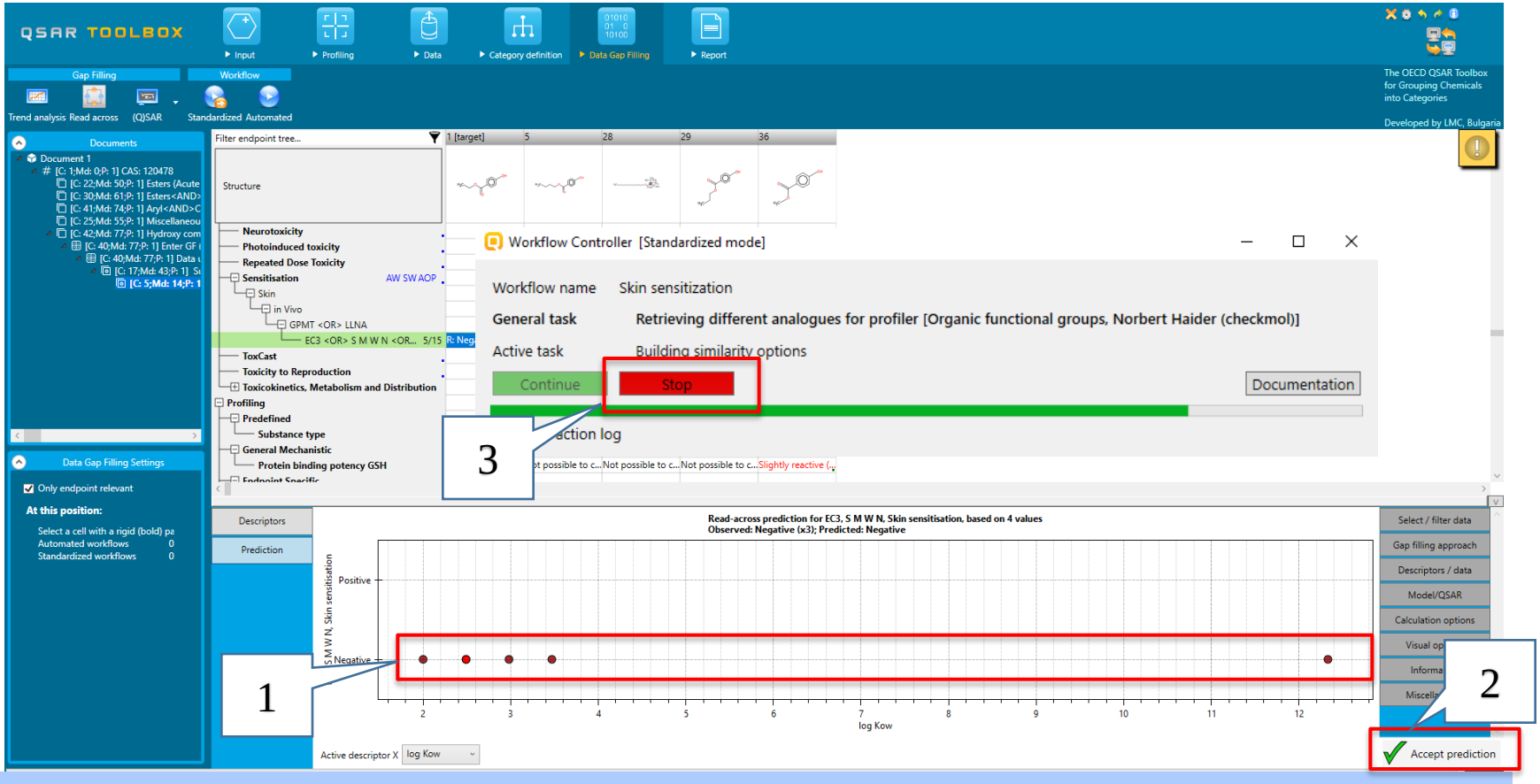
In this example we will continue with consecutive subcategorization. Click on Continue button.

Data Gap Filling
Apply Standardized workflow



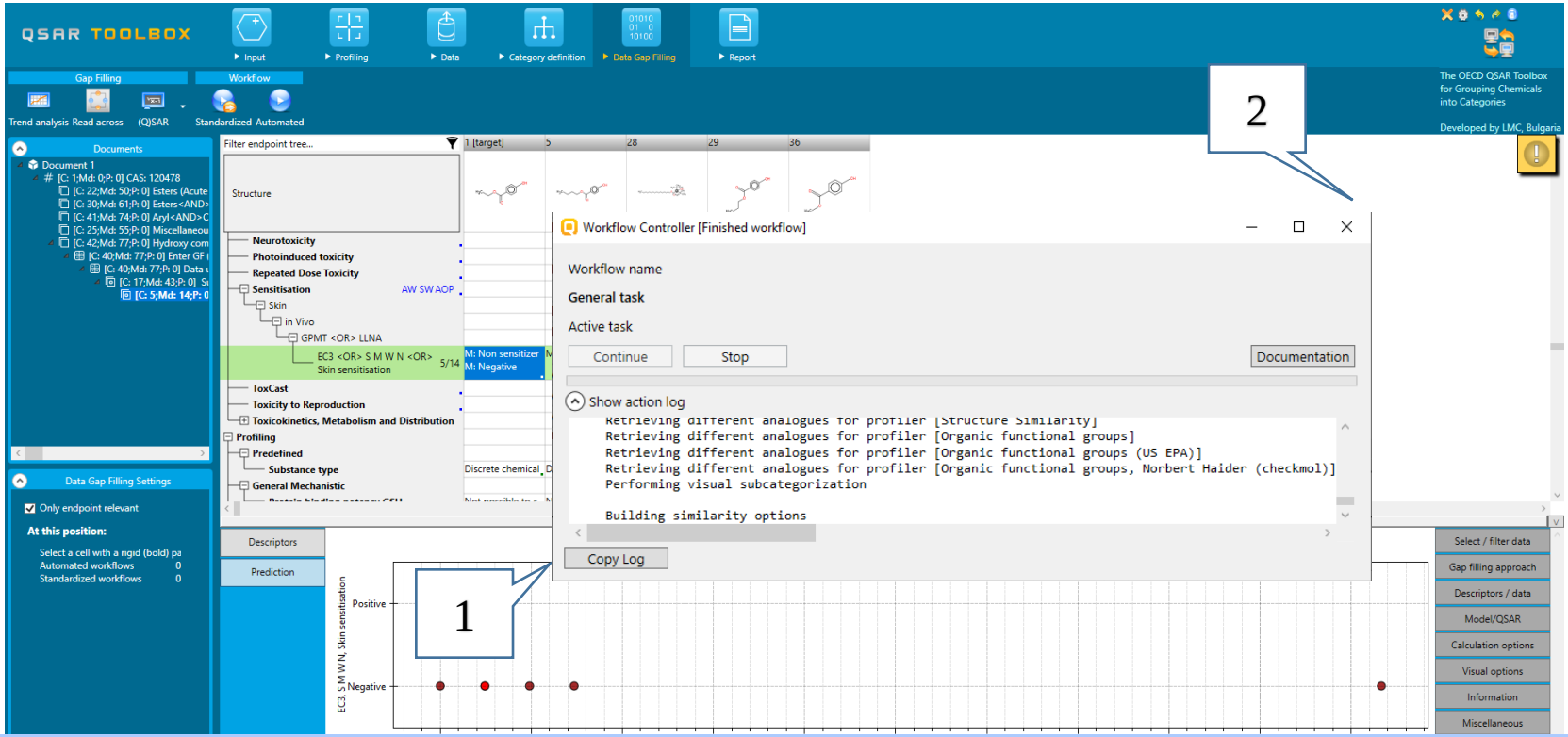
Already used profiling schemes and metabolism simulators are colored in grey (1).
Now we select ***Organic functional groups (US-EPA)*** (2) and remove the different chemicals (3).

Data Gap Filling
Apply Standardized workflow



We see that all remained chemicals after the second subcategorization possess negative data (1). The obtained result fulfilling our criteria and the prediction could be accepted (2). Therefore, we should click on the **Stop** button (3) of the workflow controller in order to stop the workflow.

Data Gap Filling
Apply Standardized workflow



The *Workflow Controller* **does not** close itself automatically. The user can expand the *activity log* (1) and to examine all performed steps during the Standardized workflow execution. After that the controller have to be closed by click on the close button (2).

Data Gap Filling
Recap

The application of the SW for skin sensitization requires user activities such as:

- specification of the endpoint;
- selection of databases;
- selection of primary grouping in case no alert is identified in the target as parent and after autoxidation and skin metabolism activation;
- selection of highlighted profiling schemes for subcategorization in order to increase the confidence of the prediction;
- accepting the prediction.

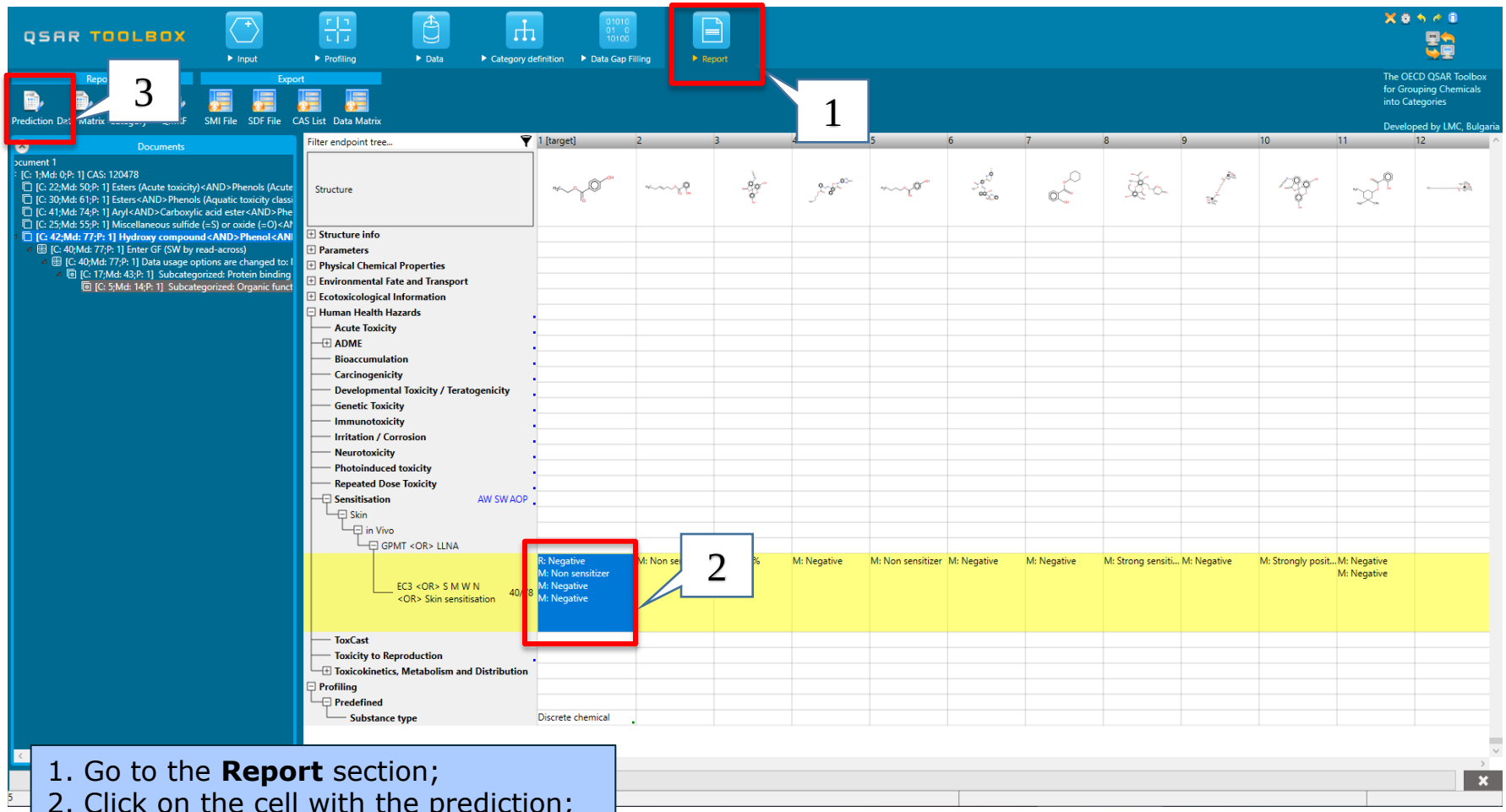
Outlook

- Background
- Keywords
- Objectives
- Specific Aims
- Read across and analogue approach
- The exercise
- **Workflow**
  - Input
  - Data Gap Filling
  - **Report**

Report
Overview

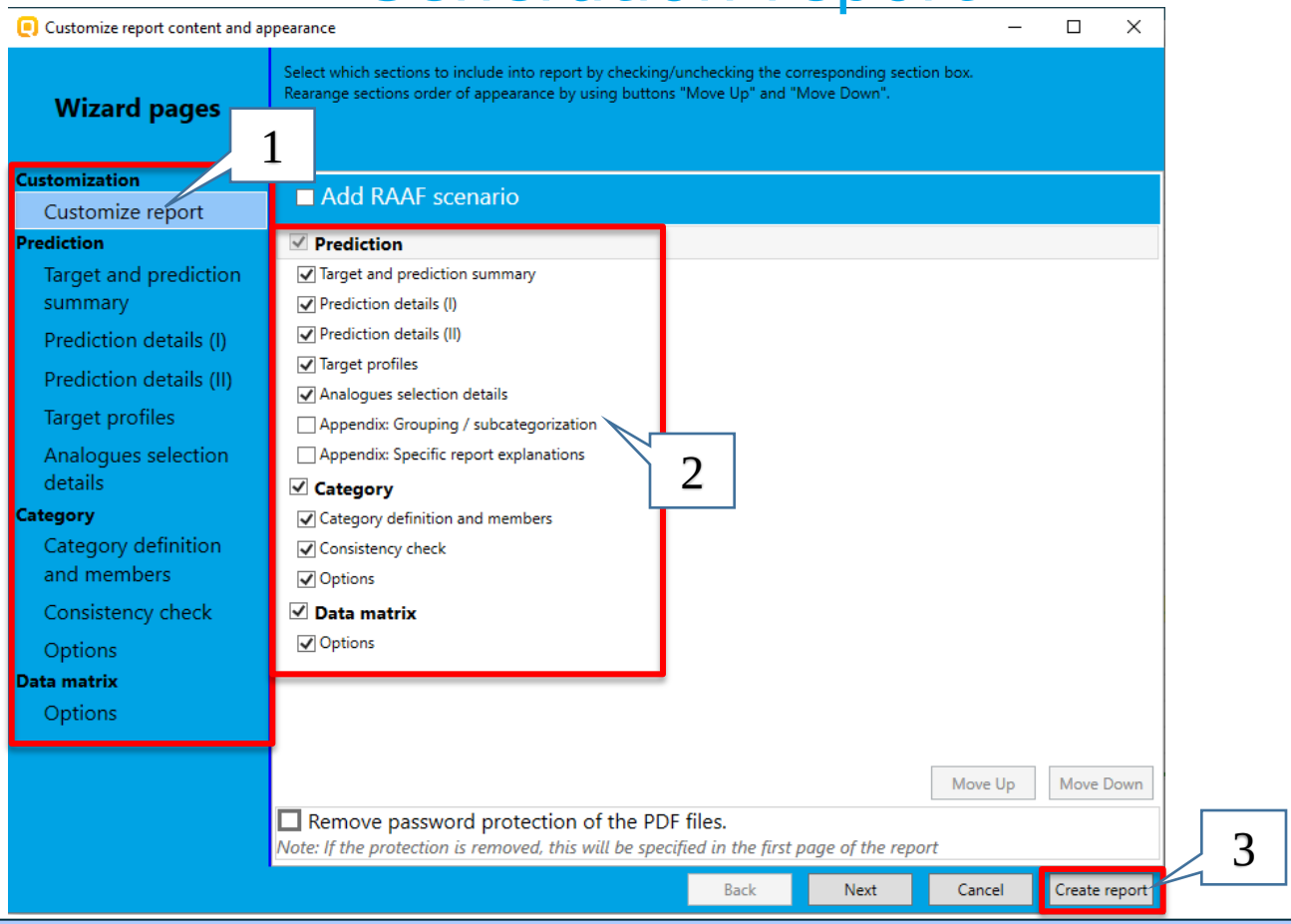
- The report module can generate reports on predictions performed with the Toolbox.
- The report module contains a predefined report template which users can customized.
- Three type of report files are generated:
  - Prediction report – containing information for the target
  - Category report – containing information for the analogues in the category
  - *Data matrix* – containing information for the analogues used for the prediction

Report
Generation report



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

Report
Generation report



The user can customize the report content (1) and appearance (2). Generation of the reports happens by click on the **Create report** button (3).

Report
Wizard pages

I. **Customized report** - the user is able to include or exclude the sections in the report;

II. **Prediction report:**

- **Target and prediction summary** – This section includes substance ID of the target chemical and the prediction outcome. Fields which are automatically populated by the system are indicated. Here the user could add information for the author, contact details and summary information;
- **Prediction details** and **Prediction details (II)** – section prediction details provides details about the prediction and its reliability. Prediction details (II) is optional it provides specific information about the prediction depending on the gap filling approach;
- **Target profiles** – this section summarize profiles used for the prediction. Additional profiles could be also included by the user;
- **Analogues selection details** – This section illustrates how analogues were selected. It displays selected databases, category boundaries and applicability domain.

Report
Wizard pages

III. Category report:

- **Category definition and members** – This part includes sections related to list of category members, basic definition of the target endpoint and category hypothesis. Also information for calculated physico-chemical parameters for the category members are provided. Some of the sections are automatically populated while for the others a report items from Report basket could be added manually.
- **Consistency check** – This part includes sections related to the layers of the consistency check: physicochemical similarity; structural similarity, mechanistic similarity and additional endpoint data. Similarly to the previous section some of the sections are automatically populated and for the others items from the Report basket could be added.;
- **Options** – in this section number of the category members used for reporting could be changed;

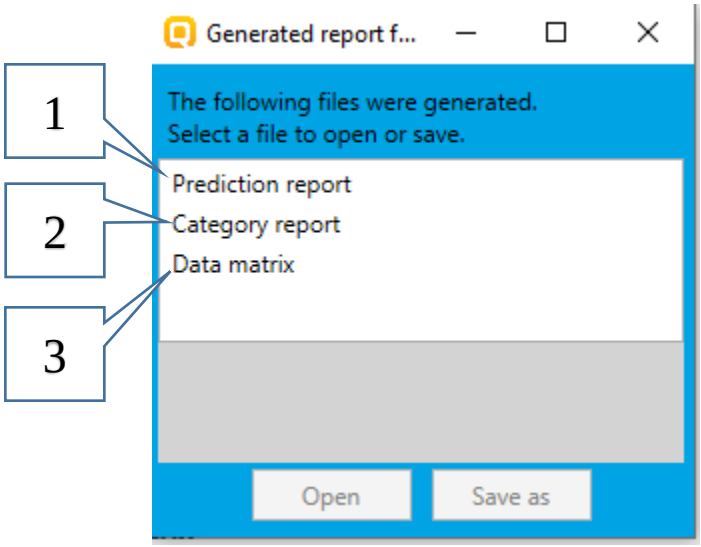
IV. Data matrix report

- Data matrix report gives the possibility to export information for the chemicals in the data matrix including parameters, profilers and experimental data.

Report
Generation report

After clicking on the Create report button, *Generated report files* window appears. It contains three types of files:

1) **Prediction report** - a PDF file containing the prediction information related to the target.
2) **Category report -** a PDF file containing information for the consistency of the final category (target plus used analogues).
3) **Data matrix** - a MS Excel file containing chemicals used for prediction along with their data for selected parameters, profiles and endpoint tree positions.

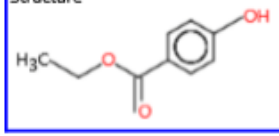


Report
Generated report files

Prediction report

QSAR Toolbox prediction for single chemical

Date: 14 Apr 2020
Author(s):
Contact details:

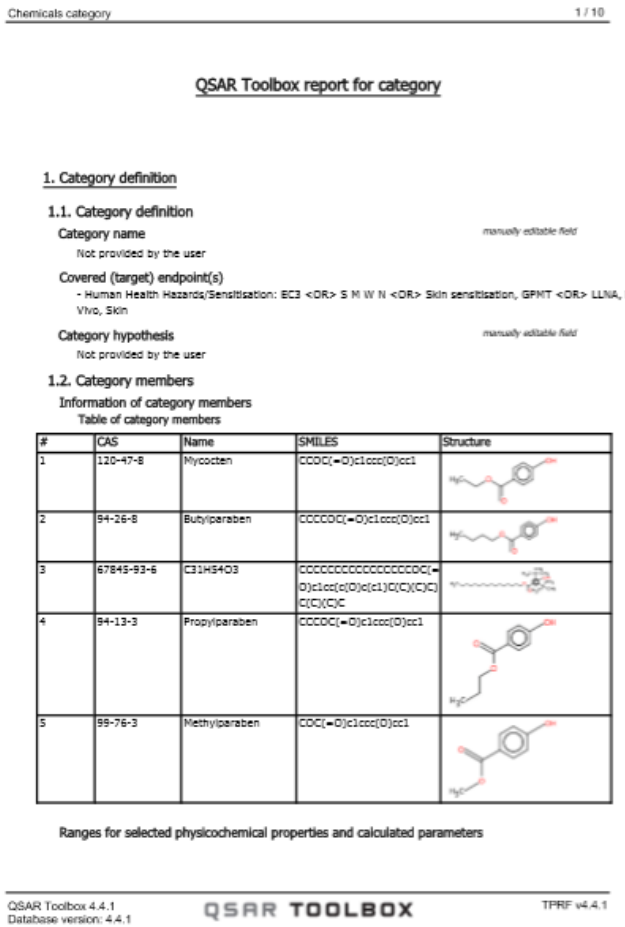
Target information		
Structural information	**Numerical identifiers**	**Chemical names**
SMILES: CCOC(=O)c1ccc(O)cc1 Structure 	CAS#: 120-47-8 Other: EC Number:2043994	4-hydroxybenzoic aci d ethyl ester 4-hydroxy-benzoic ac id ethyl ester 4-hydroxybenzoic aci d, ethyl ester

Prediction summary
Predicted endpoint: EC3, S M W N, Skin sensitisation; No effect specified; No species specified; No duration specified; No guideline specified
Predicted value: Negative
~~**Unit/scale:** Skin sensitisation II (ECETOC)~~
Data gap filling method: Read-across analysis
Summary: *manually editable field* Not provided by the user

Using of a standardized workflow for predicting of skin sensitization potential is noted in the *Prediction report*.

Report
Category report files

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 <OR> S M W N <OR> Skin sensitisation, GPMT <OR> LLNA, In Vivo, Skin

Category hypothesis *manually editable field*

Not provided by the user

1.2. Category members

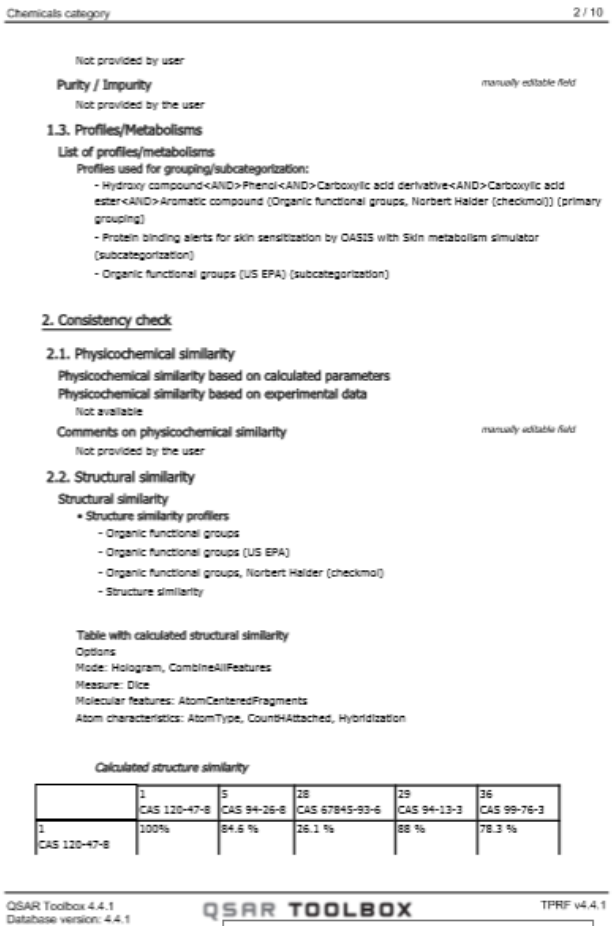
Information of category members

Table of category members

#	CAS	Name	SMILES	Structure
1	120-47-8	Mycocten	CCOC(=O)c1ccc(O)cc1	
2	94-26-8	Butylparaben	CCCCOC(=O)c1ccc(O)cc1	
3	67845-93-6	C31H54O3	CCCCCCCCCCCCCCCCOC(=O)c1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C	
4	94-13-3	Propylparaben	CCCOC(=O)c1ccc(O)cc1	
5	99-76-3	Methylparaben	COC(=O)c1ccc(O)cc1	

Ranges for selected physicochemical properties and calculated parameters

QSAR Toolbox 4.4.1
Database version: 4.4.1
QSAR TOOLBOX
TPRF v4.4.1



Chemicals category 2 / 10

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:

- Hydroxy compound<AND>Phenol<AND>Carboxylic acid derivative<AND>Carboxylic acid ester<AND>Aromatic compound (Organic functional groups, Norbert Haider (checkmol)) (primary grouping)
- Protein binding alerts for skin sensitization by OASIS with Skin metabolism simulator (subcategorization)
- Organic functional groups (US EPA) (subcategorization)

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

- Structure similarity profilers
  - Organic functional groups
  - Organic functional groups (US EPA)
  - Organic functional groups, Norbert Haider (checkmol)
  - Structure similarity

Table with calculated structural similarity

Options

Mode: Hologram, CombineAllFeatures

Measure: Dice

Molecular features: AtomCenteredFragments

Atom characteristics: AtomType, CountHAttached, Hybridization

Calculated structure similarity

	1 CAS 120-47-8	5 CAS 94-26-8	28 CAS 67845-93-6	29 CAS 94-13-3	36 CAS 99-76-3
1 CAS 120-47-8	100%	84.6 %	26.1 %	88 %	78.3 %

QSAR Toolbox 4.4.1
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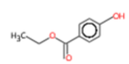
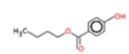
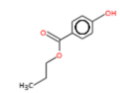
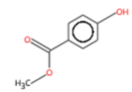
Information for the members of the category obtained as a result of AW application is included in the Category *report*.

Report
Data matrix files

Data matrix report

	Target chemical			Neighbour #3	Neighbour #4
Substance identity					
Structure					
CAS number	120-47-8	94-26-8	67845-93-6	94-13-3	99-76-3
Chemical name	Mycocten	Butylparaben	C31H54O3	Propylparaben	Methylparaben
Other identifier					
SMILES	CCOC(=O)c1ccc(O)cc1	CCCCOC(=O)c1ccc(O)cc1	CCCCCCCCCCCCCCCCOC(=O)c1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C	CCCOC(=O)c1ccc(O)cc1	COC(=O)c1ccc(O)cc1
Parameters unit					
Profilers					
Profiles used for grouping/subcategorization					
Hydroxy compound<AND>Phenol<AND>Carboxylic acid derivative<AND>Carboxylic acid ester<AND>Aromatic compound (Organic functional groups, Norbert Haider (checkmol))	Hydroxy compound; Phenol; Carboxylic acid derivative; Carboxylic acid ester; Aromatic compound	Hydroxy compound; Phenol; Carboxylic acid derivative; Carboxylic acid ester; Aromatic compound	Hydroxy compound; Phenol; Carboxylic acid derivative; Carboxylic acid ester; Aromatic compound	Hydroxy compound; Phenol; Carboxylic acid derivative; Carboxylic acid ester; Aromatic compound	Hydroxy compound; Phenol; Carboxylic acid derivative; Carboxylic acid ester; Aromatic compound
Protein binding alerts for skin sensitization by	No alert found	No alert found	No alert found	No alert found	No alert found
Organic functional groups (US EPA) (subcategorization)	Aliphatic Carbon [CH]; Aliphatic Carbon [-CH2-]; Aliphatic Carbon [-CH3]; Aromatic Carbon [C]; Carbonyl, one aromatic attach [-C(=O)-]; Ester, aliphatic attach [-C(=O)O]; Hydroxy, aromatic attach [-OH]; Miscellaneous sulfide (=S) or oxide (=O); Olefinic carbon [=CH- or =C<]; Oxygen, one aromatic attach [-O-]	Aliphatic Carbon [CH]; Aliphatic Carbon [-CH2-]; Aliphatic Carbon [-CH3]; Aromatic Carbon [C]; Carbonyl, one aromatic attach [-C(=O)-]; Ester, aliphatic attach [-C(=O)O]; Hydroxy, aromatic attach [-OH]; Miscellaneous sulfide (=S) or oxide (=O); Olefinic carbon [=CH- or =C<]; Oxygen, one aromatic attach [-O-]	Aliphatic Carbon [CH]; Aliphatic Carbon [-CH2-]; Aliphatic Carbon [-CH3]; Aromatic Carbon [C]; Carbonyl, one aromatic attach [-C(=O)-]; Ester, aliphatic attach [-C(=O)O]; Hydroxy, aromatic attach [-OH]; Miscellaneous sulfide (=S) or oxide (=O); Olefinic carbon [=CH- or =C<]; Oxygen, one aromatic attach [-O-]	Aliphatic Carbon [CH]; Aliphatic Carbon [-CH2-]; Aliphatic Carbon [-CH3]; Aromatic Carbon [C]; Carbonyl, one aromatic attach [-C(=O)-]; Ester, aliphatic attach [-C(=O)O]; Hydroxy, aromatic attach [-OH]; Miscellaneous sulfide (=S) or oxide (=O); Olefinic carbon [=CH- or =C<]; Oxygen, one aromatic attach [-O-]	Aliphatic Carbon [CH]; Aliphatic Carbon [-CH2-]; Aliphatic Carbon [-CH3]; Aromatic Carbon [C]; Carbonyl, one aromatic attach [-C(=O)-]; Ester, aliphatic attach [-C(=O)O]; Hydroxy, aromatic attach [-OH]; Miscellaneous sulfide (=S) or oxide (=O); Olefinic carbon [=CH- or =C<]; Oxygen, one aromatic attach [-O-]
Predefined					
Substance type	Discrete chemical; Organic; Mono constituent (predefined)	Discrete chemical; Organic; Mono constituent (predefined)	Discrete chemical; Organic; Mono constituent (predefined)	ERROR!	ERROR!
General Mechanistic					
Protein binding potency GSH	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Slightly reactive (GSH) >> Reaction at sp3 carbon atom (SN2)

Analogues used for the target prediction can be seen the **Data matrix** report. Their selected profiling results, experimental data and/or parameters are also shown.

Congratulations!

- You have completed the tutorial on the standardized workflow for skin sensitization data gap filling.

- You have now been introduced to the consecutive steps of the standardized workflow of the (Q)SAR Toolbox and the rationale behind each step.

- Note, proficiency comes with practice!