QSAR Toolbox functionalities.
Alert performance.

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Category definition

Alert performance (AP)

Usability

- Alert performance is used to define how much relevant to a target endpoint an alert is.
- Alert performance could be applied also to any profile categories; e.g., to organic functional group
- The reliability of alerts is context dependent and is significantly affected by target endpoint, selected databases, calculation mode (i.e., data usage) and data scale.

Category definition

Alert performance (AP)

Requirements

- Calculation of Alert performance is allowed **only** if the target endpoint is defined.
- It is applicable **only** to categorical endpoints, i.e., for endpoints whose experimental data are defined as categories, e.g. *Strong*, *Weak*, *Non*; *Positive*, *Negative*, etc.

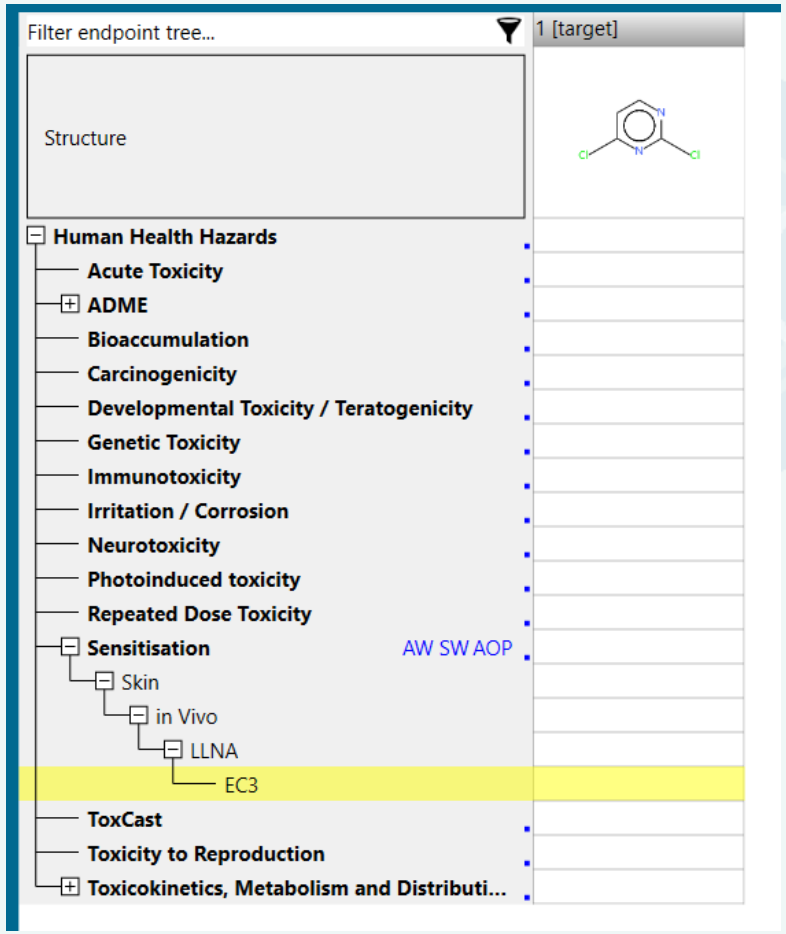
Category definition

Alert performance (AP)

Example

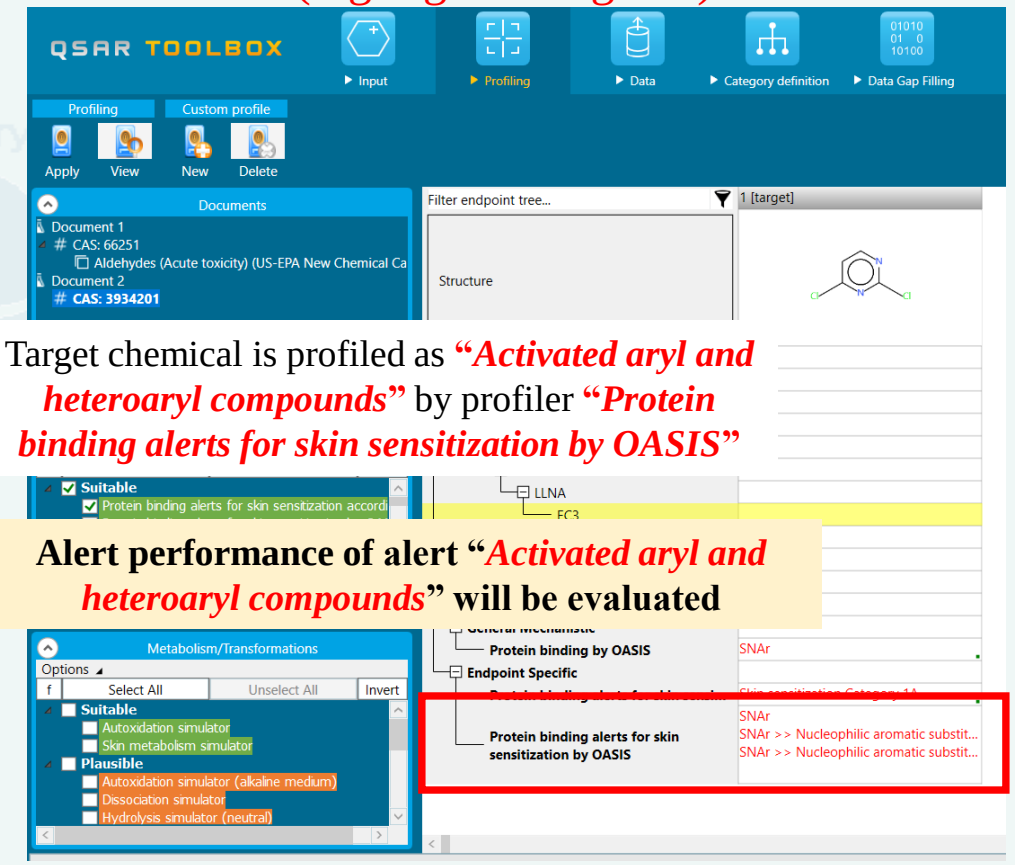
Target chemical: CAS 3934-20-1

Target endpoint: *in vivo* Skin Sensitization, LLNA, EC3



Profiling results

Profiling results by the relevant profilers (highlighted in green):



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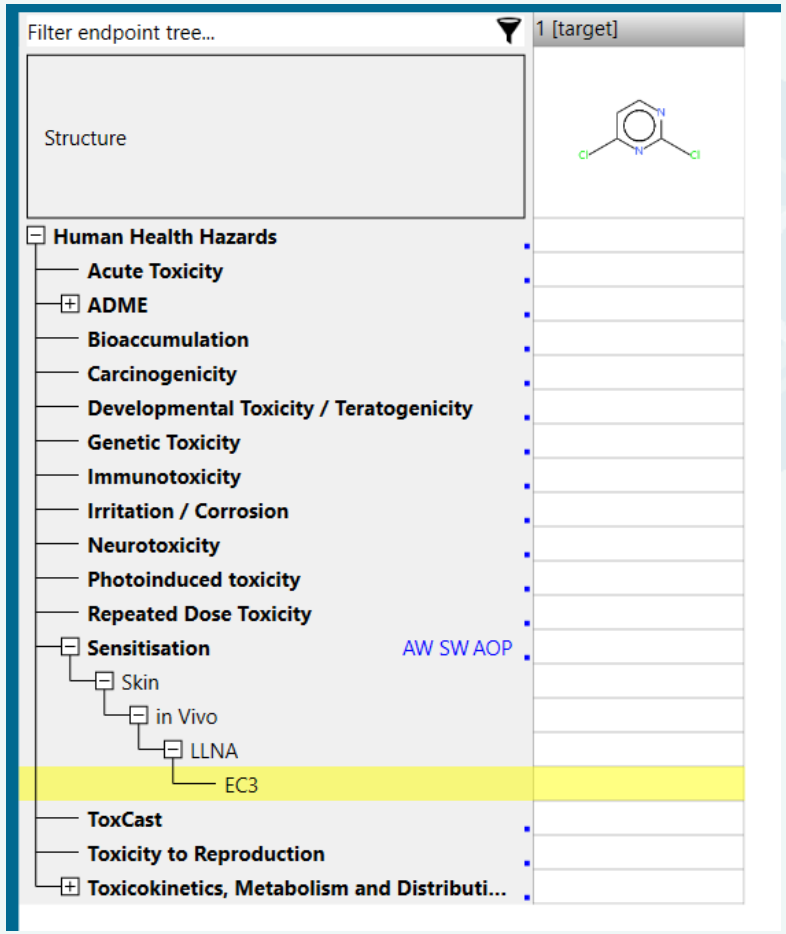
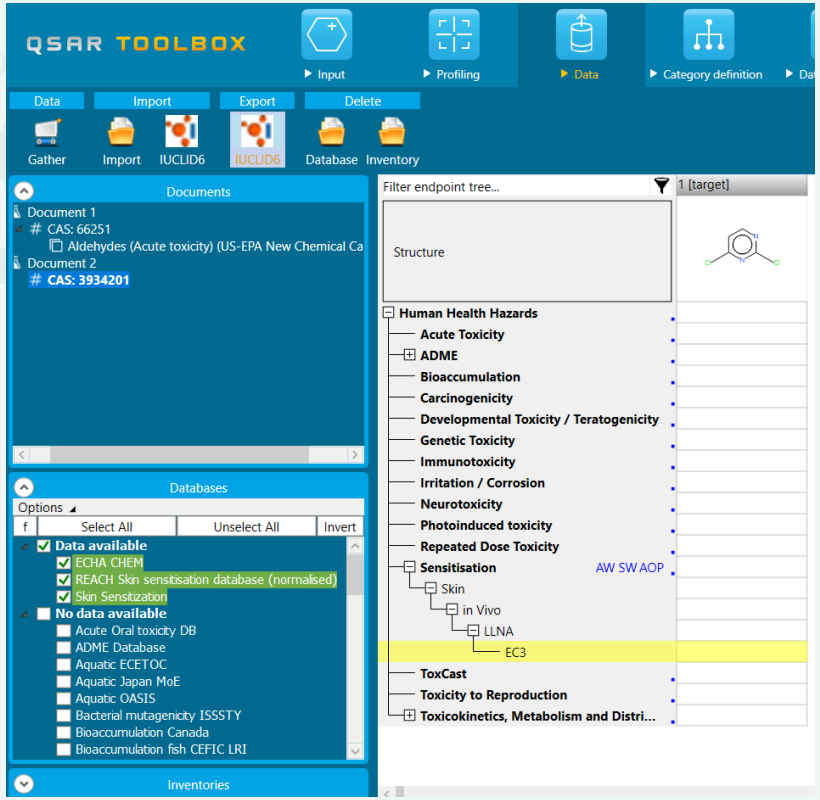


Databases

The databases having experimental data for the target endpoint need to be selected (highlighted in green):



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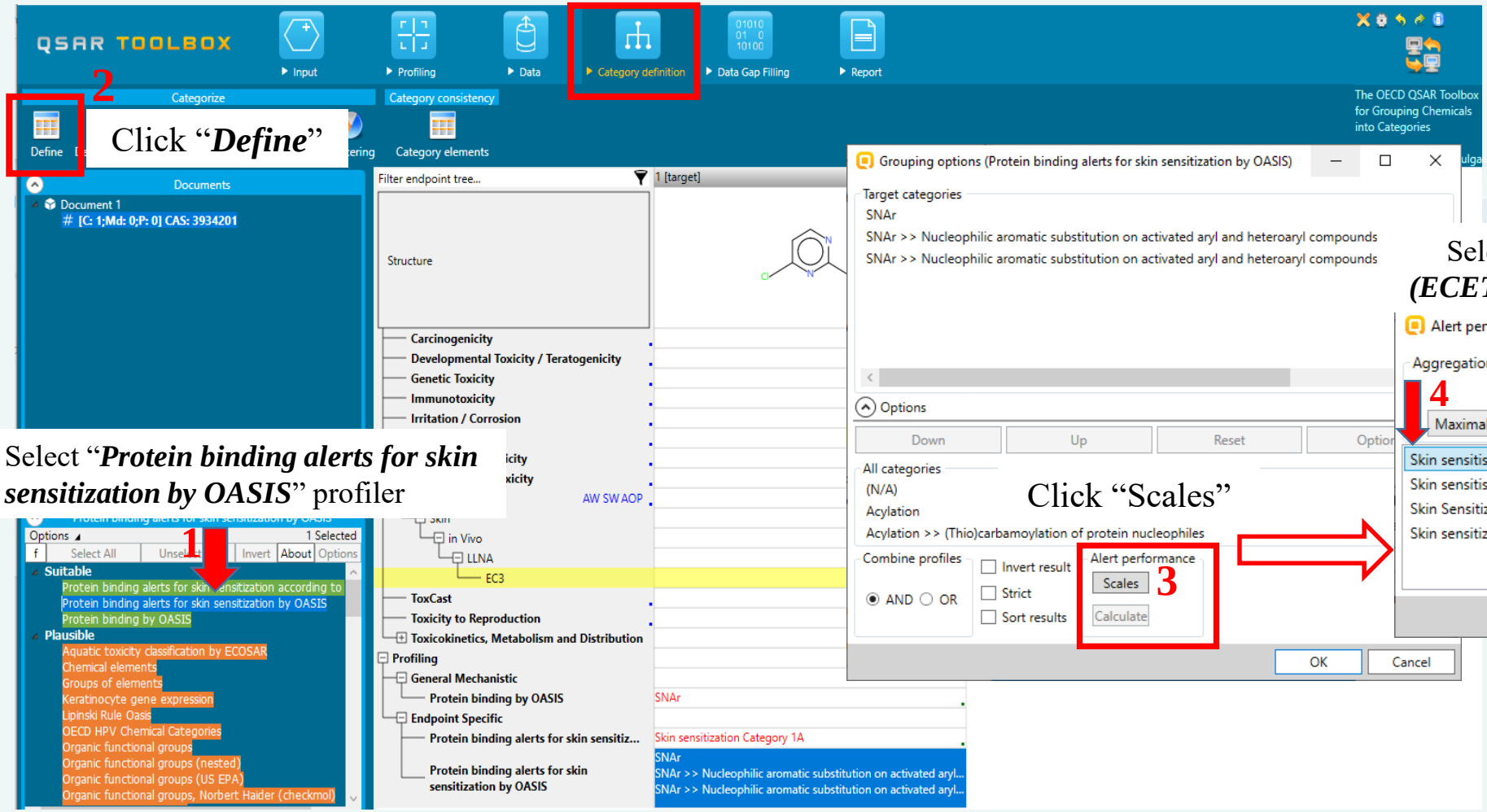

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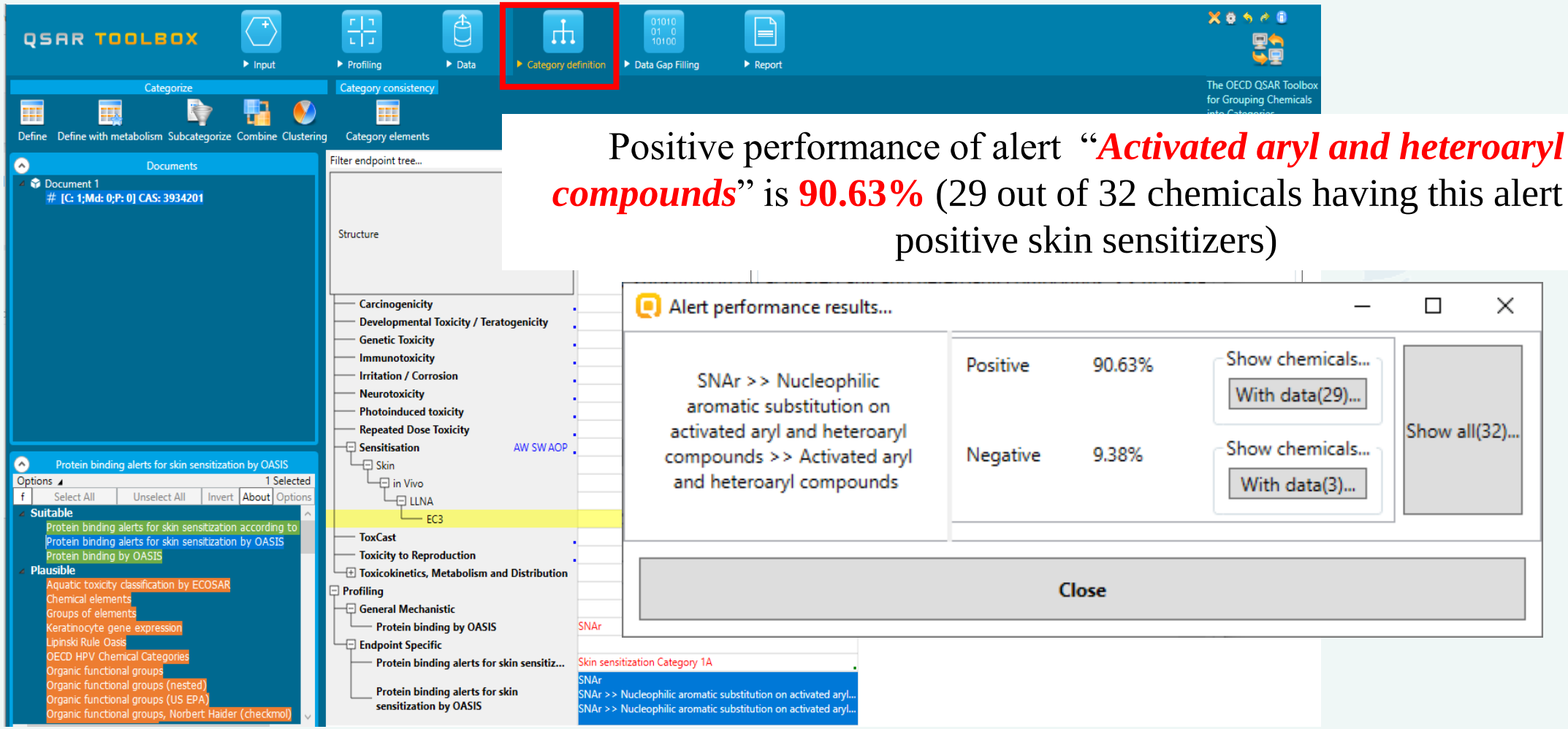


Positive performance of alert "***Activated aryl and heteroaryl compounds***" is **90.63%** (29 out of 32 chemicals having this alert are positive skin sensitizers)

Category definition

Alert performance (AP)

Problems resolved by AP:

- Searching for SAR
- Selecting alerts in case of polyfunctional chemicals
- Identification of conservative alert
- Adjusting alert

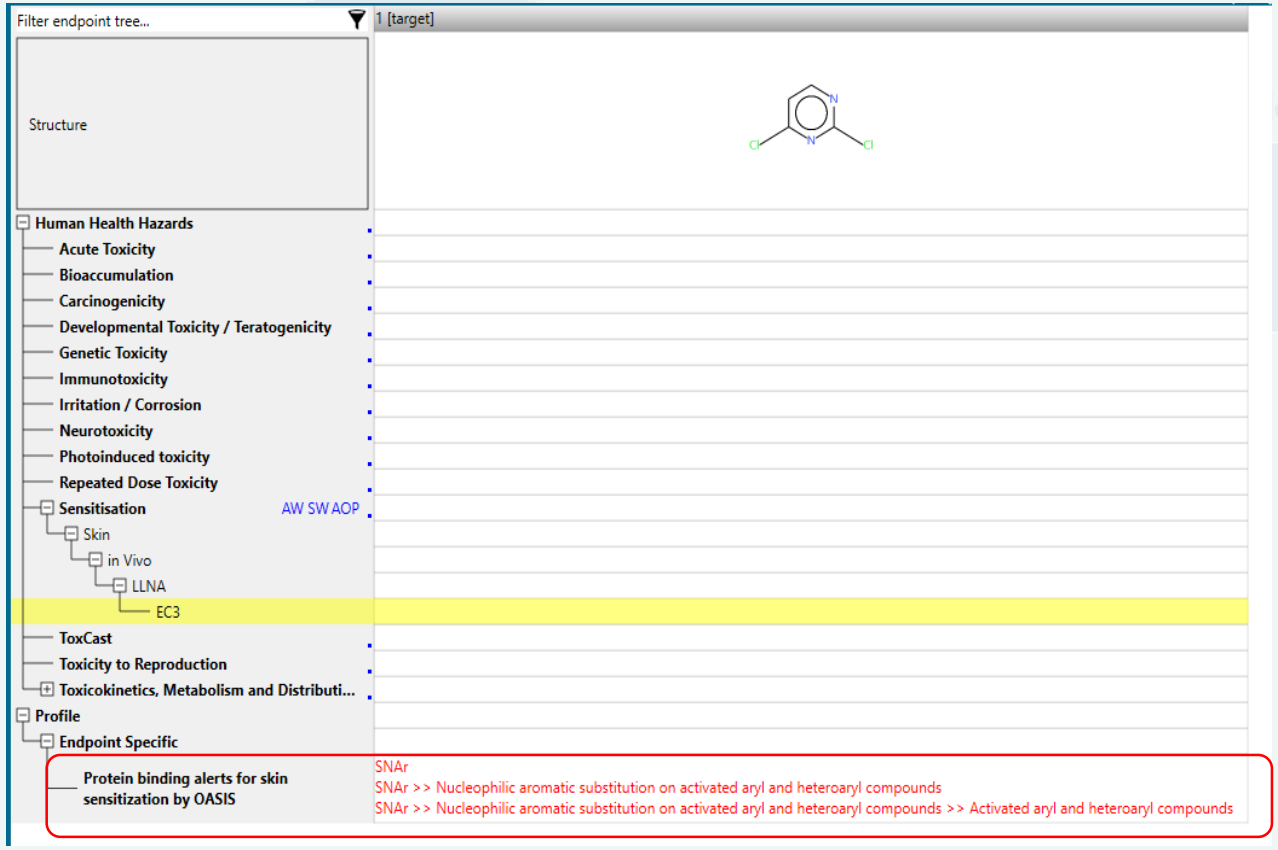
Category definition

Alert performance (AP)

Problems resolved by AP:

1) Is the alert a SAR?

Example: CAS 3934-20-1 – Protein binding alert for SS is identified



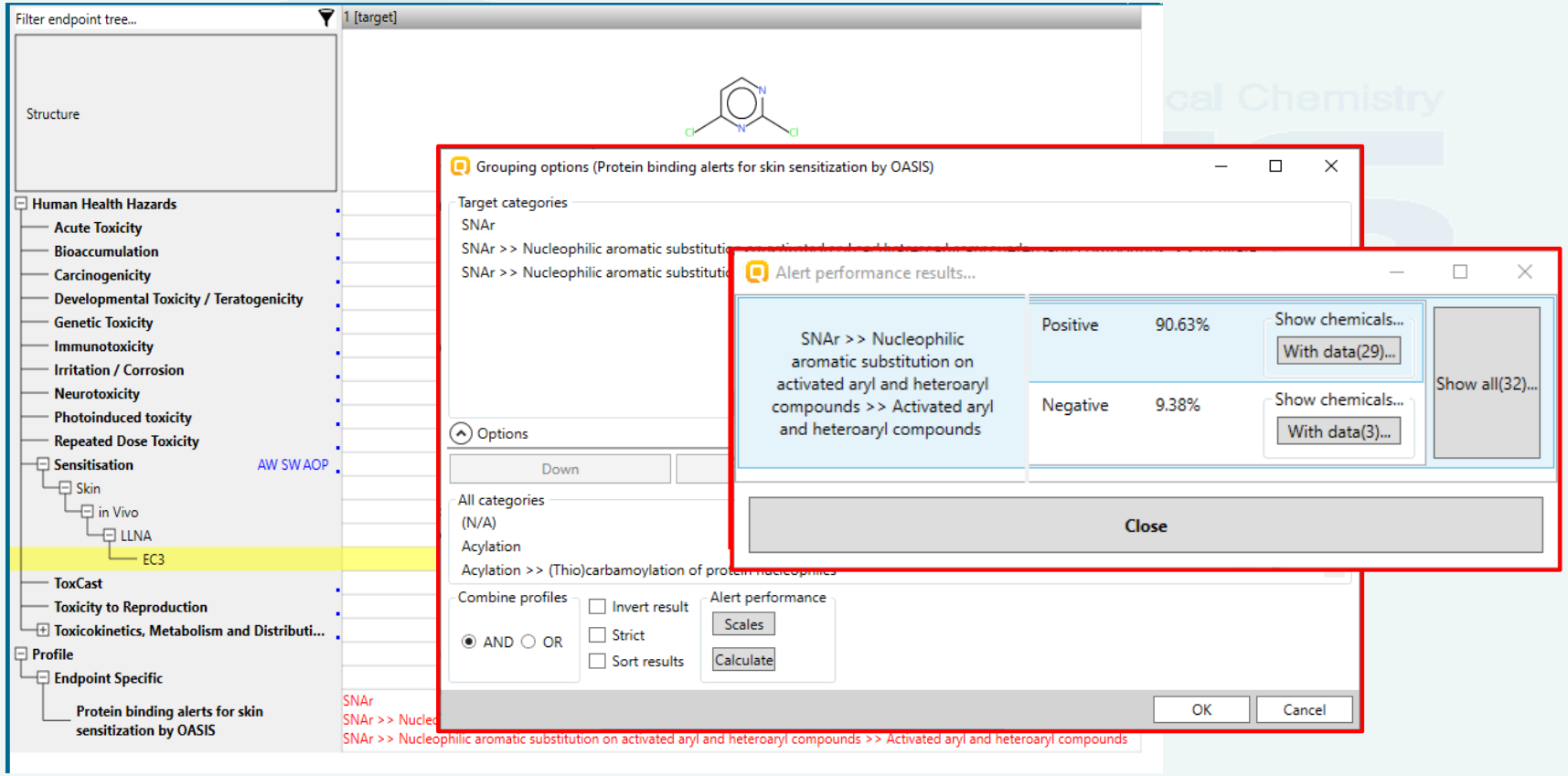
Category definition

Alert performance (AP)

Problems resolved by AP:

1) Is the alert a SAR? – **This is a SAR!**

Example: CAS 3934-20-1 – 90% of chemicals with this alert have positive experimental data



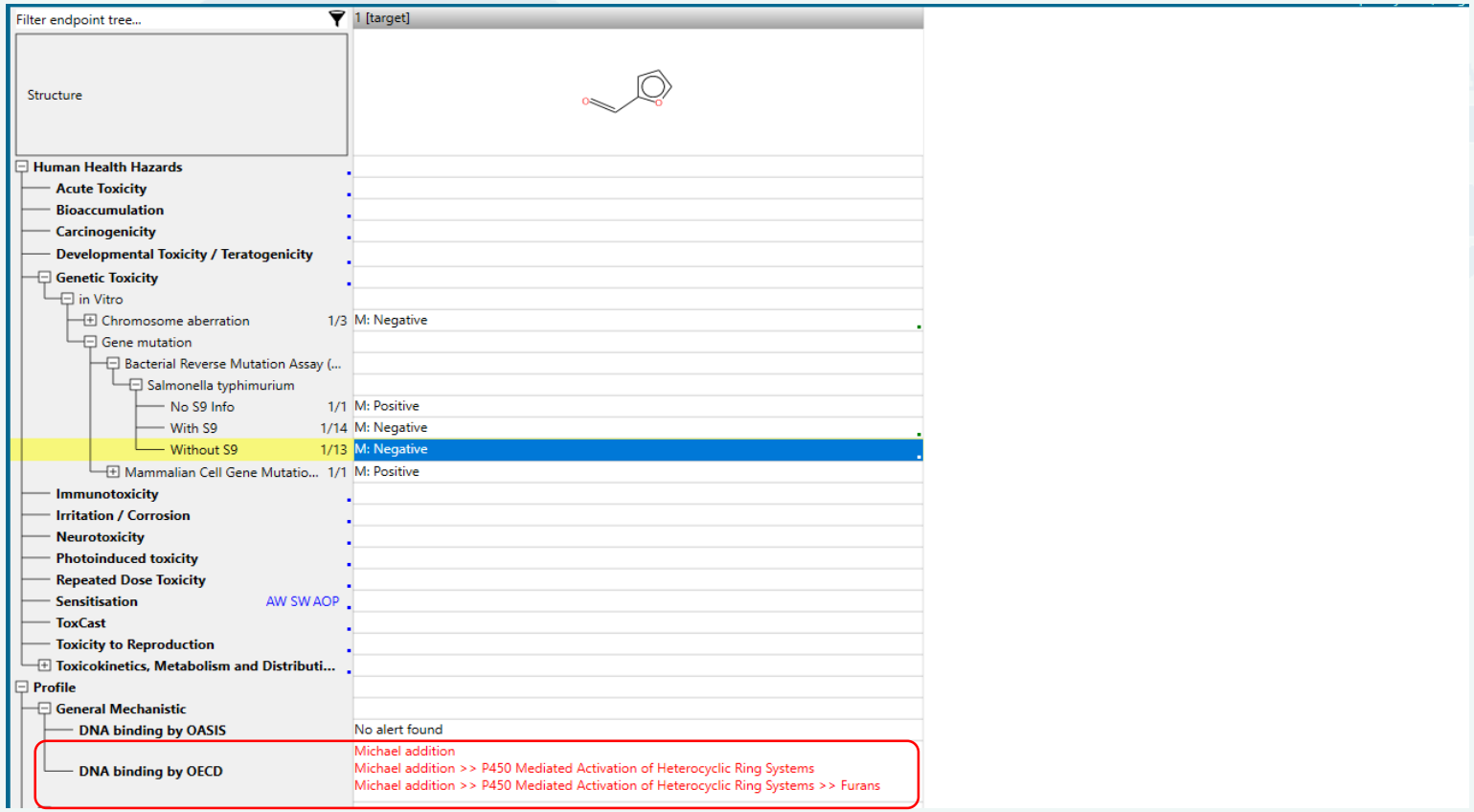
Category definition

Alert performance (AP)

Problems resolved by AP:

2) Identification of “conservative” alerts - specific for a selected chemical and endpoint

Example: CAS 98-01-1 Furfural – DNA binding alert is identified



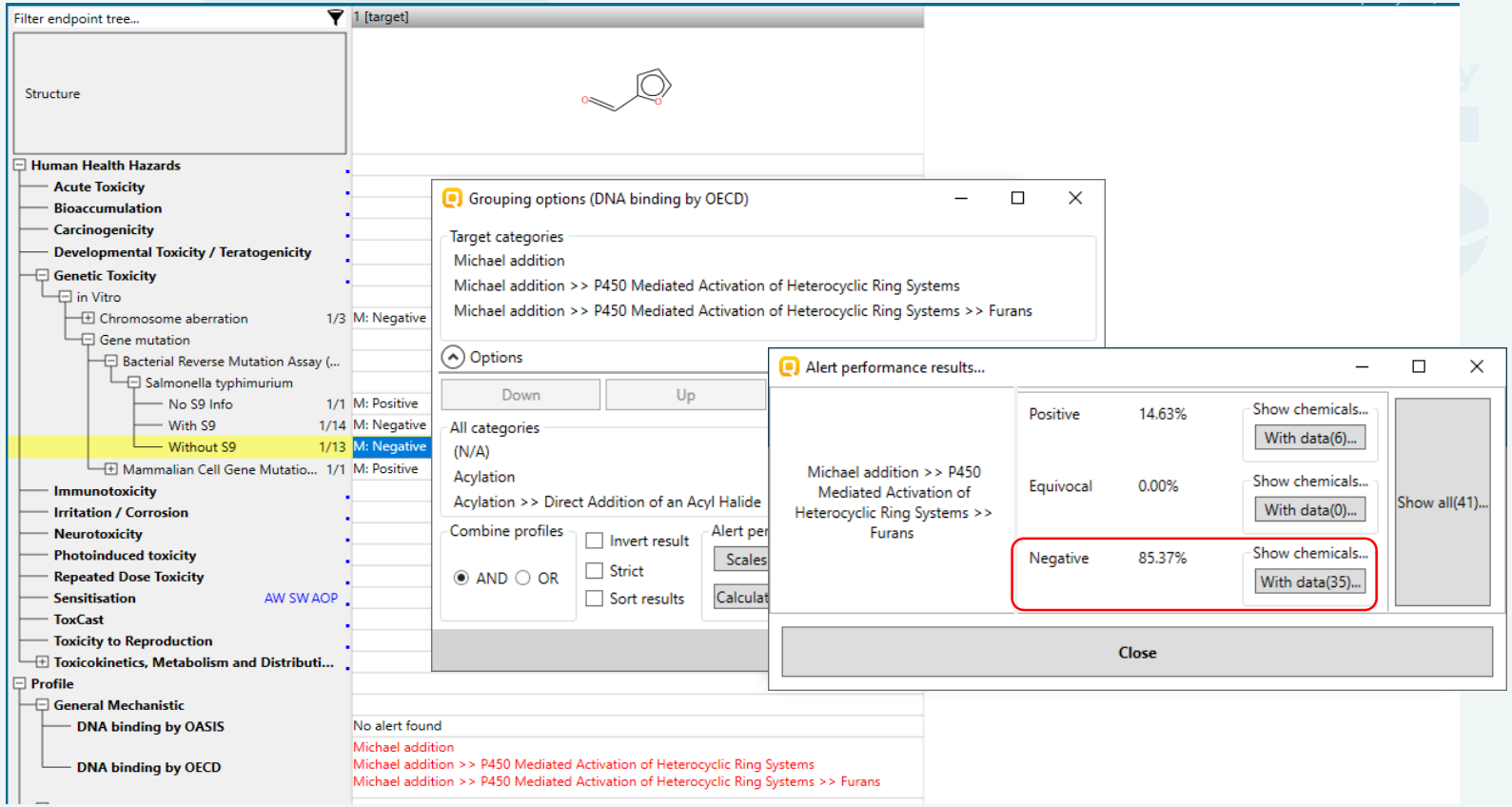
Category definition

Alert performance (AP)

Problems resolved by AP:

2) Identification of “conservative” alerts - specific for a chemical and endpoint

Example: CAS 98-01-1 Furfural – Low performance of the identified alert from DNA binding profile for CAS 98-01-1



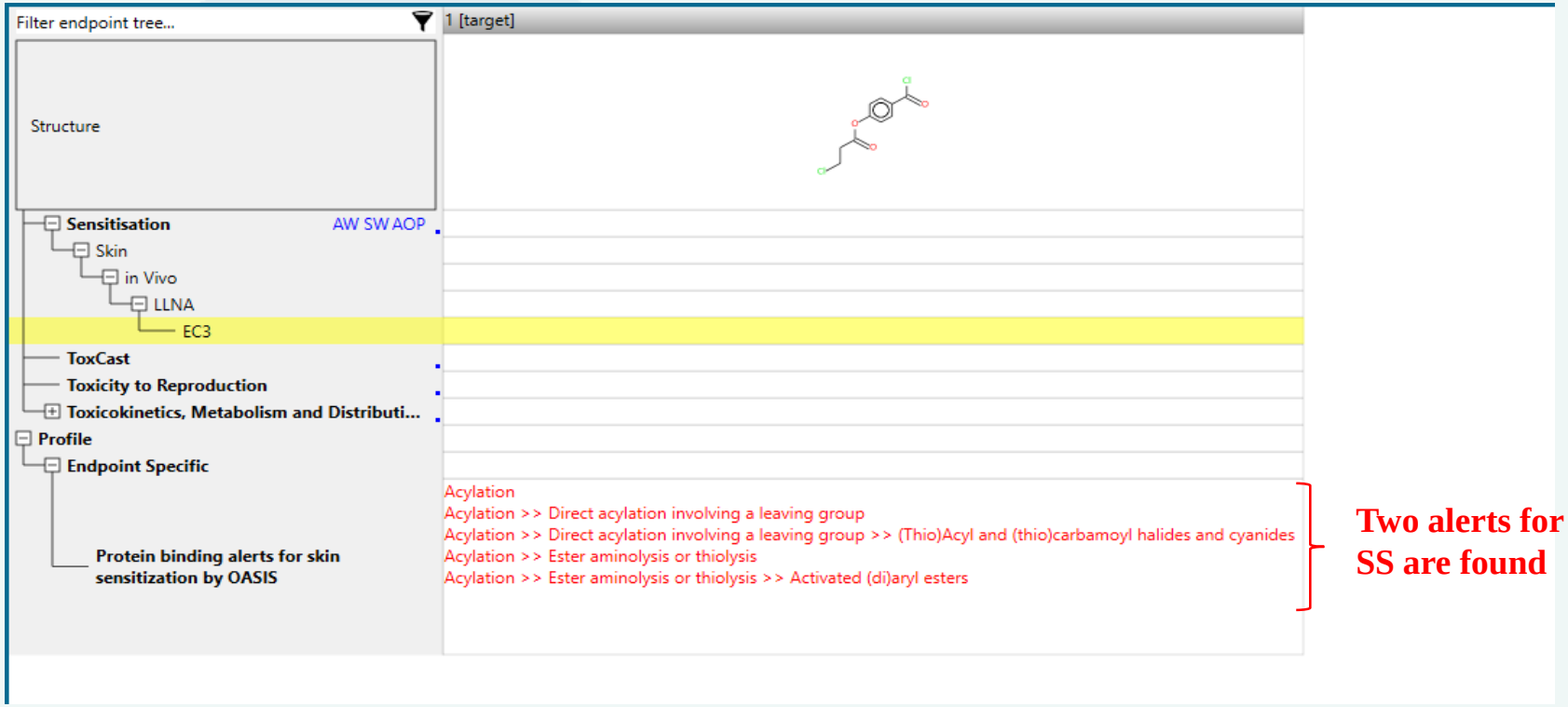
Category definition

Alert performance (AP)

Problems resolved by AP:

3) Selection of alert in case of polyfunctional chemicals

Example: CAS 366448-53-5 – two protein binding alerts for SS are identified



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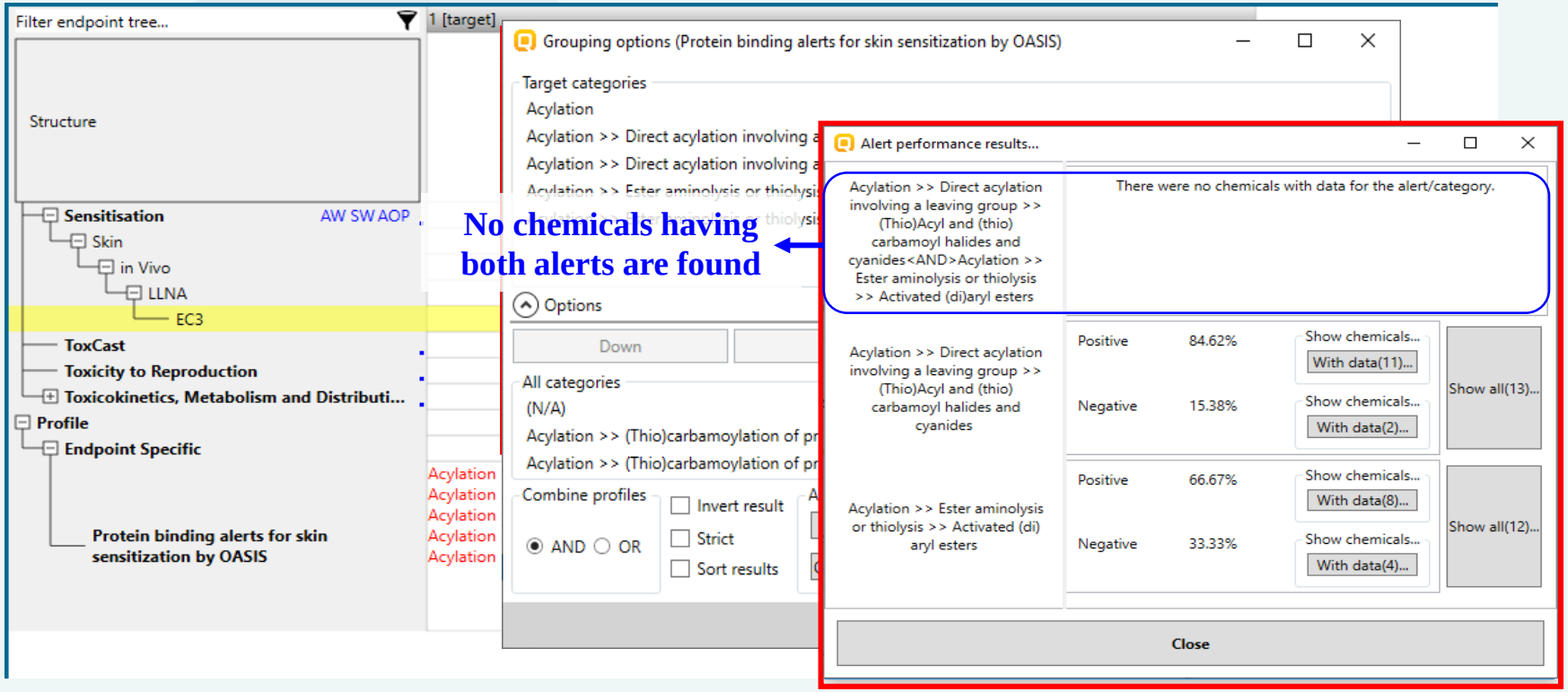


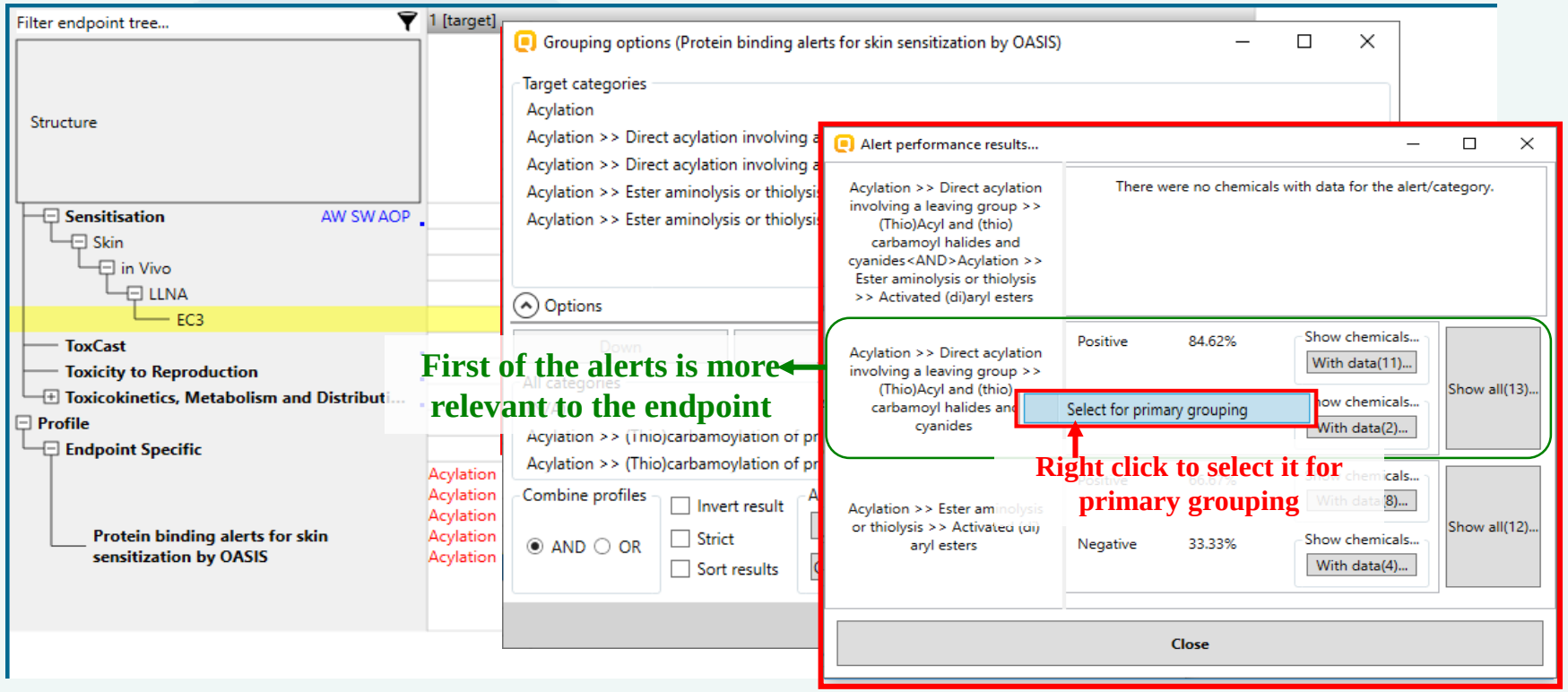
Category definition

Alert performance (AP)

Problems resolved by AP:

3) Selection of alert in case of polyfunctional chemicals

Example: CAS 366448-53-5 – two protein binding alerts for SS are identified **– giving preference to one of them**



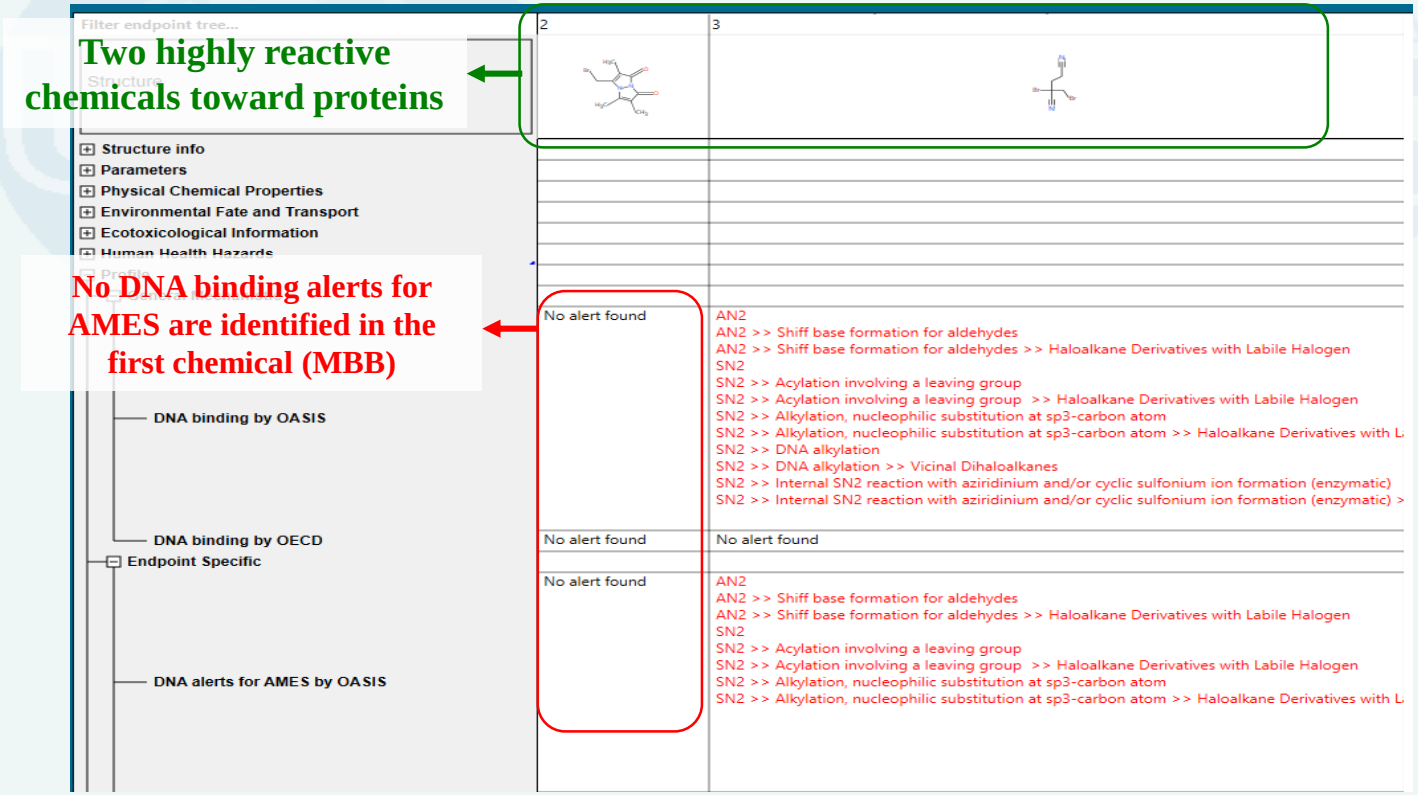
Category definition

Alert performance (AP)

Problems resolved by AP:

4) Adjusting alert boundaries

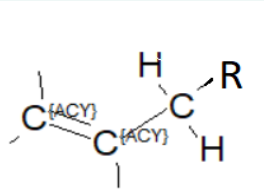
a. Analysis of profiling result of two structures that are hypothesized to have same mechanism of interaction with DNA



Category definition

Alert performance (AP)

Original structural boundary of DNA "Haloalkane" alert



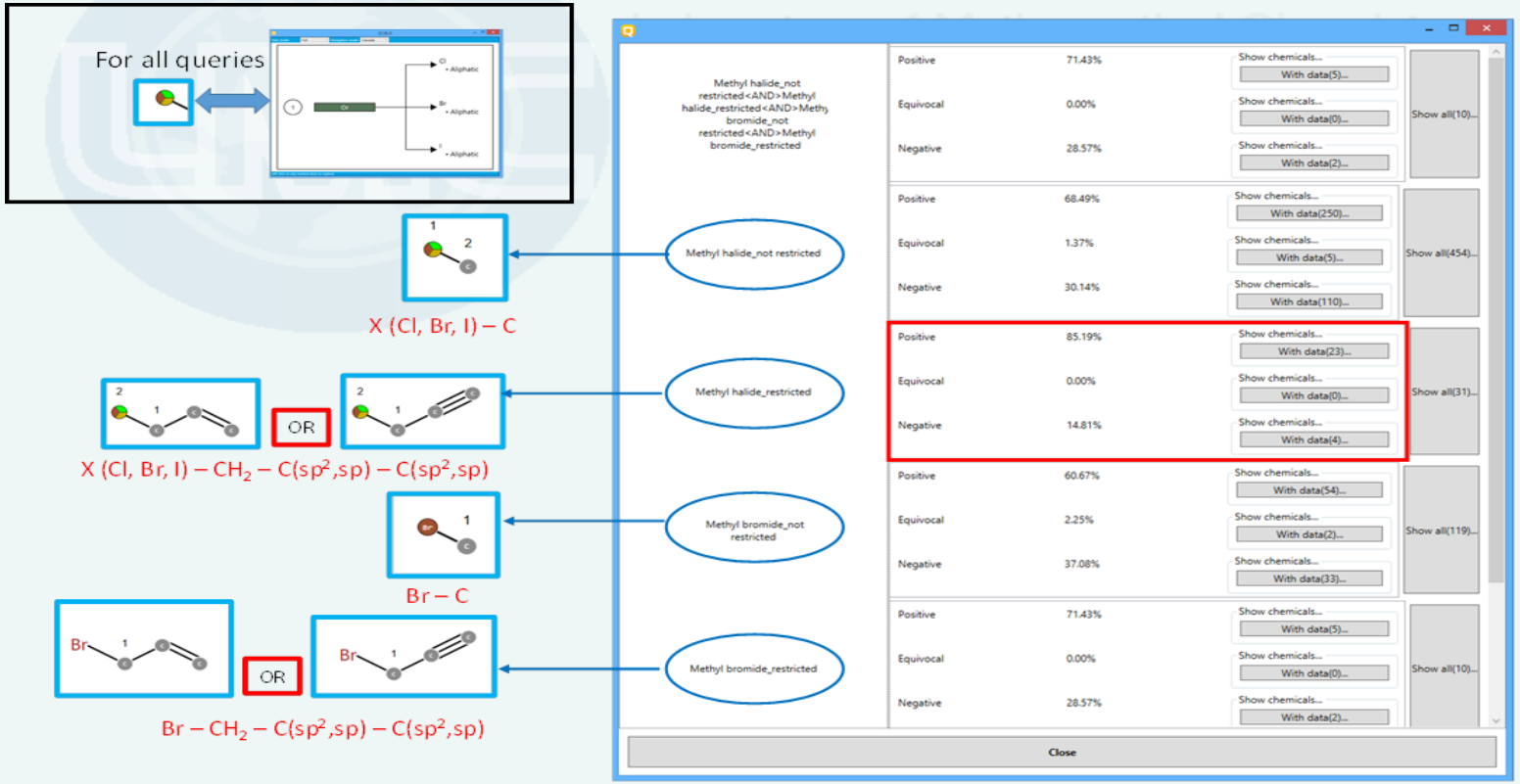
R = Cl, Br, I

Problems resolved by AP:

4) Adjusting alert boundaries

b. Analysis of available data by searching of chemicals with modified "*Haloalkane*" alerts

AP with respect to DNA-binding using AMES –S9 data was calculated for the following boundaries:



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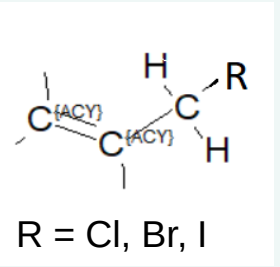


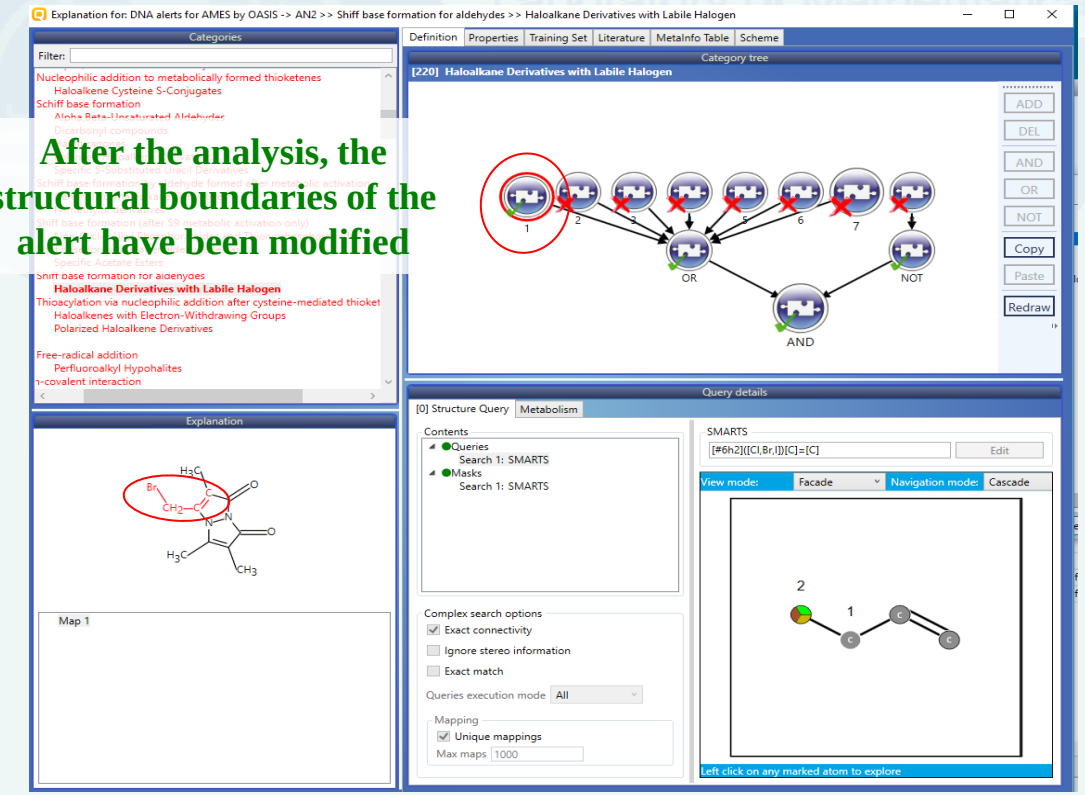
R = Cl, Br, I

Problems resolved by AP:

4) Adjusting alert boundaries

c. Adjusting the structural boundaries of the DNA "*Haloalkane*" alert – **specificity for "acycling" C-atoms was removed**

Profiling result for MBB by the new (modified) DNA "Haloalkane" alert

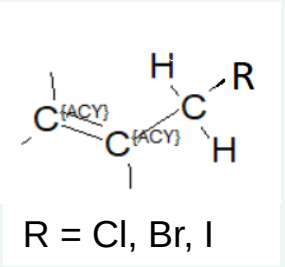


After the analysis, the structural boundaries of the alert have been modified

Category definition

Alert performance (AP)

Original structural boundary of DNA "Haloalkane" alert



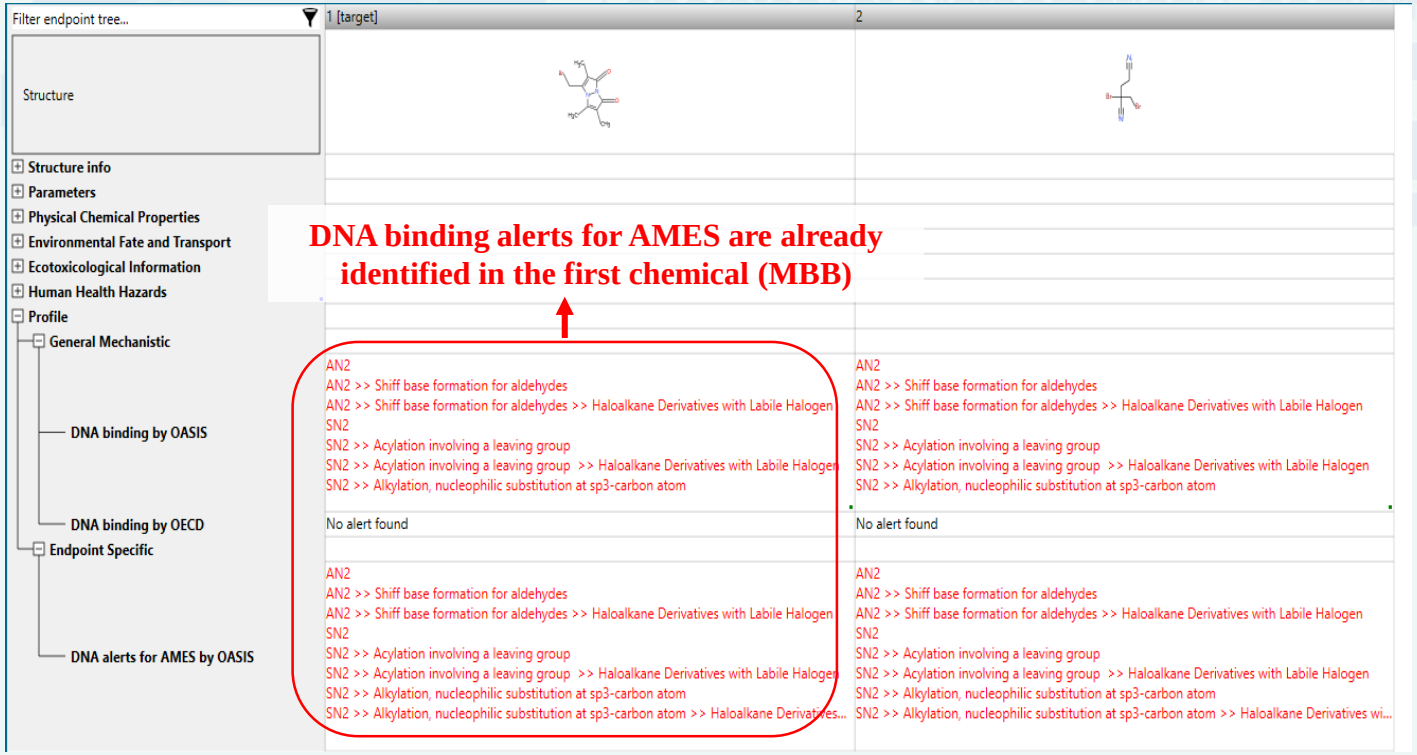
R = Cl, Br, I

Problems resolved by AP:

4) Adjusting alert boundaries

c. Adjusting the structural boundaries of the DNA "*Haloalkane*" alert – **specificity for "acycling" C-atoms was removed**

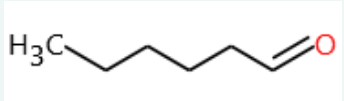
Profiling result for MBB by the DNA alerts for AMES by OASIS



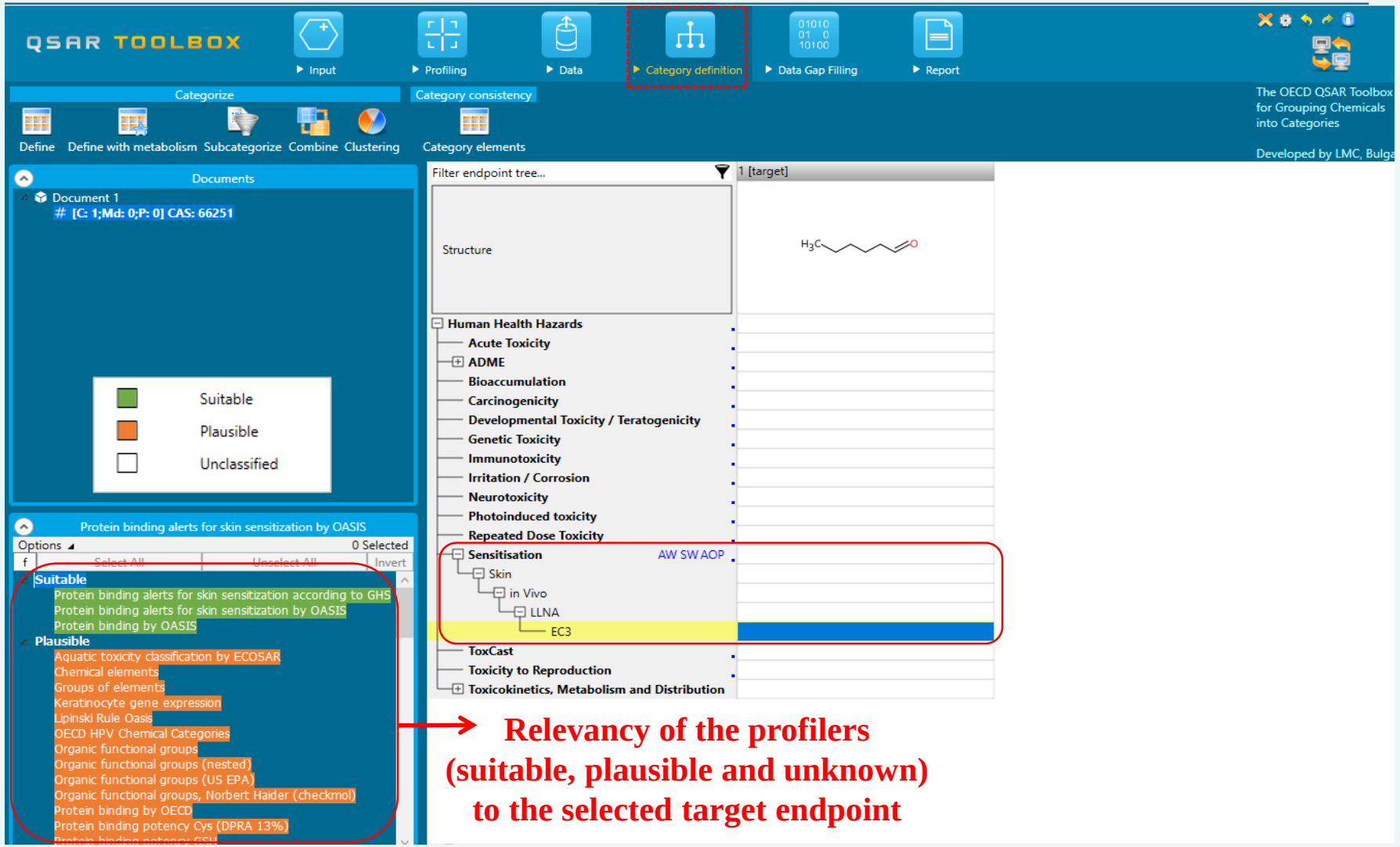
Category definition

Alert performance (AP) – without metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization



CAS 66-25-1



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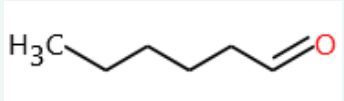

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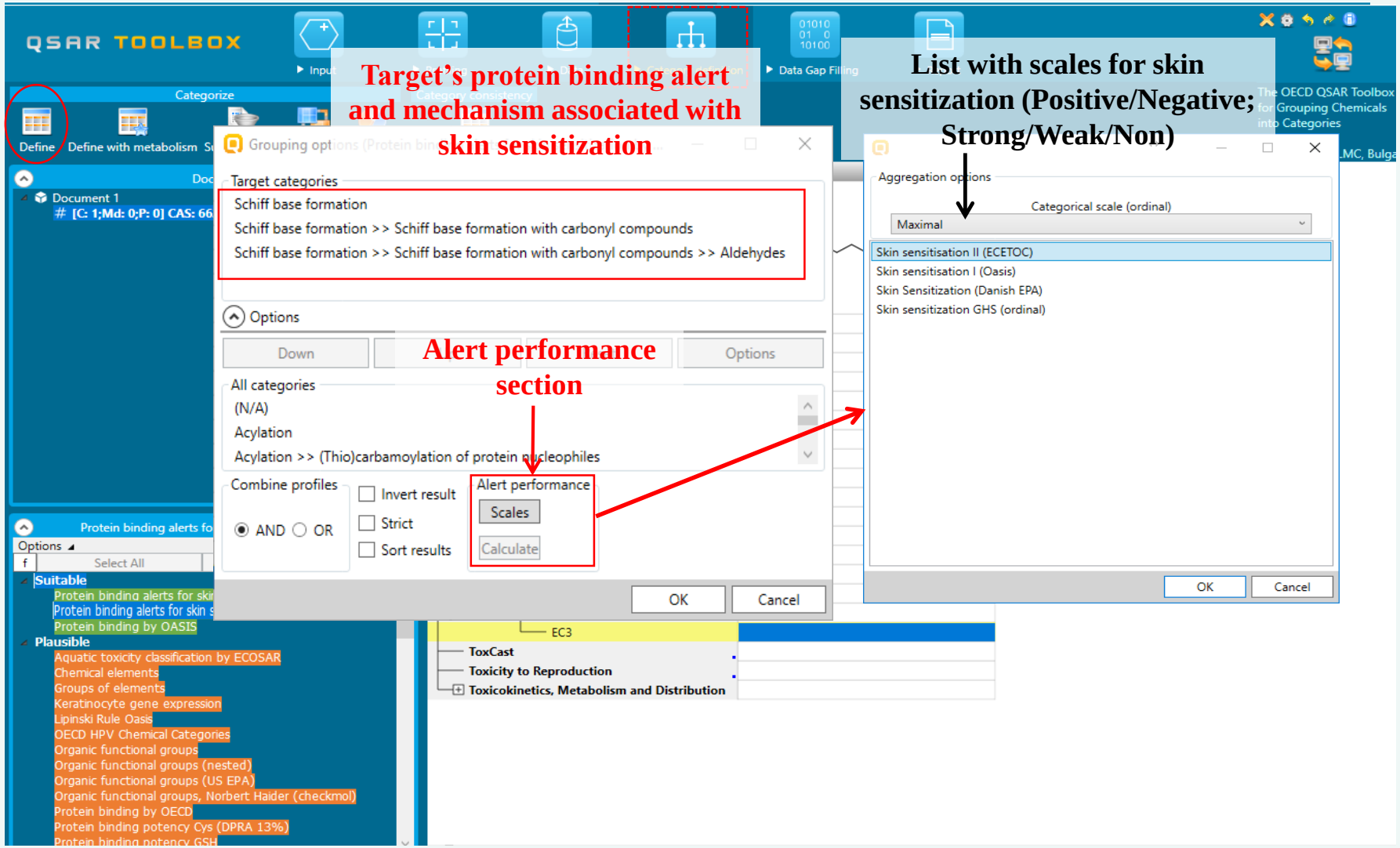

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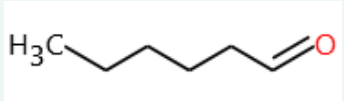

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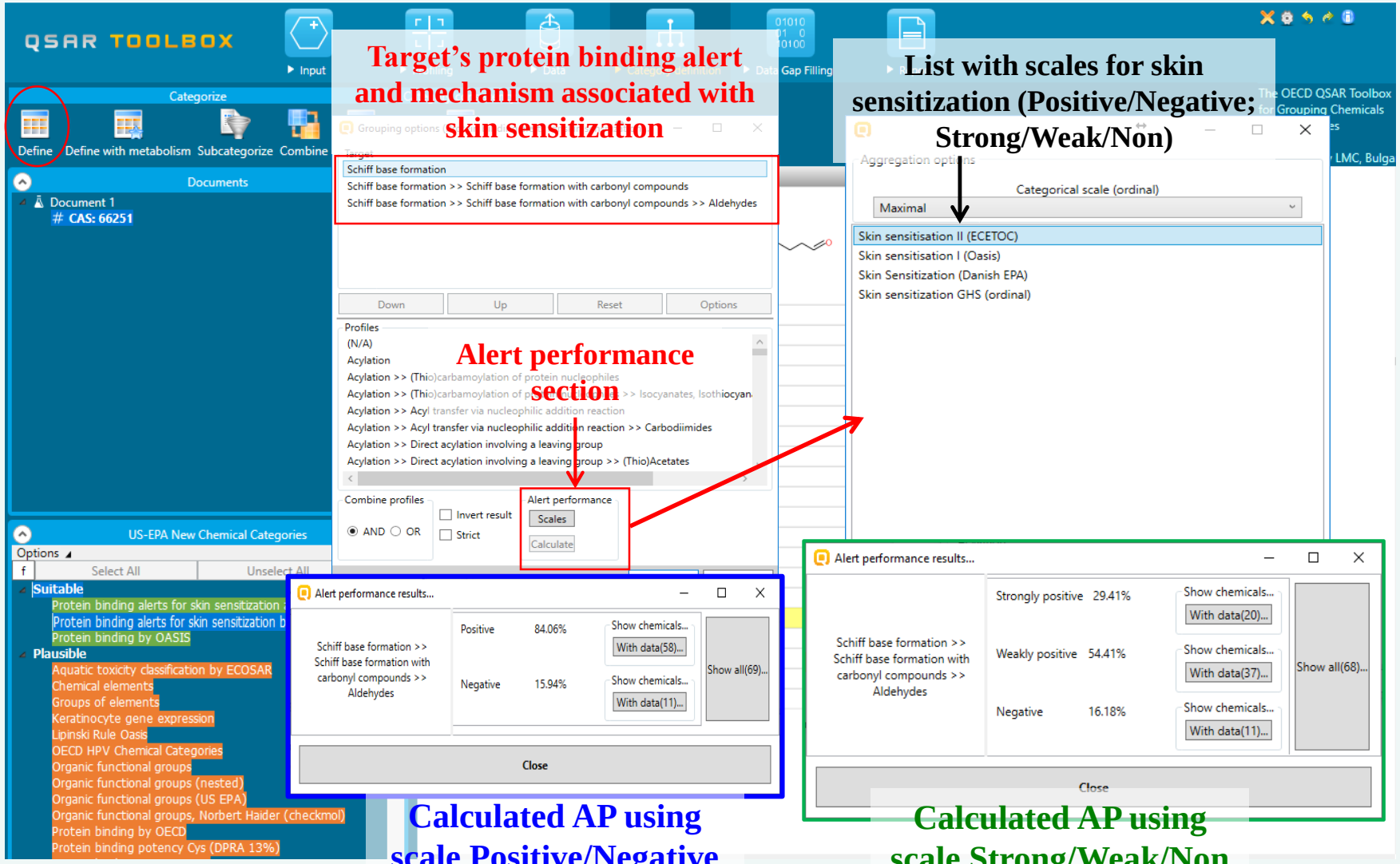
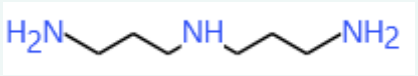


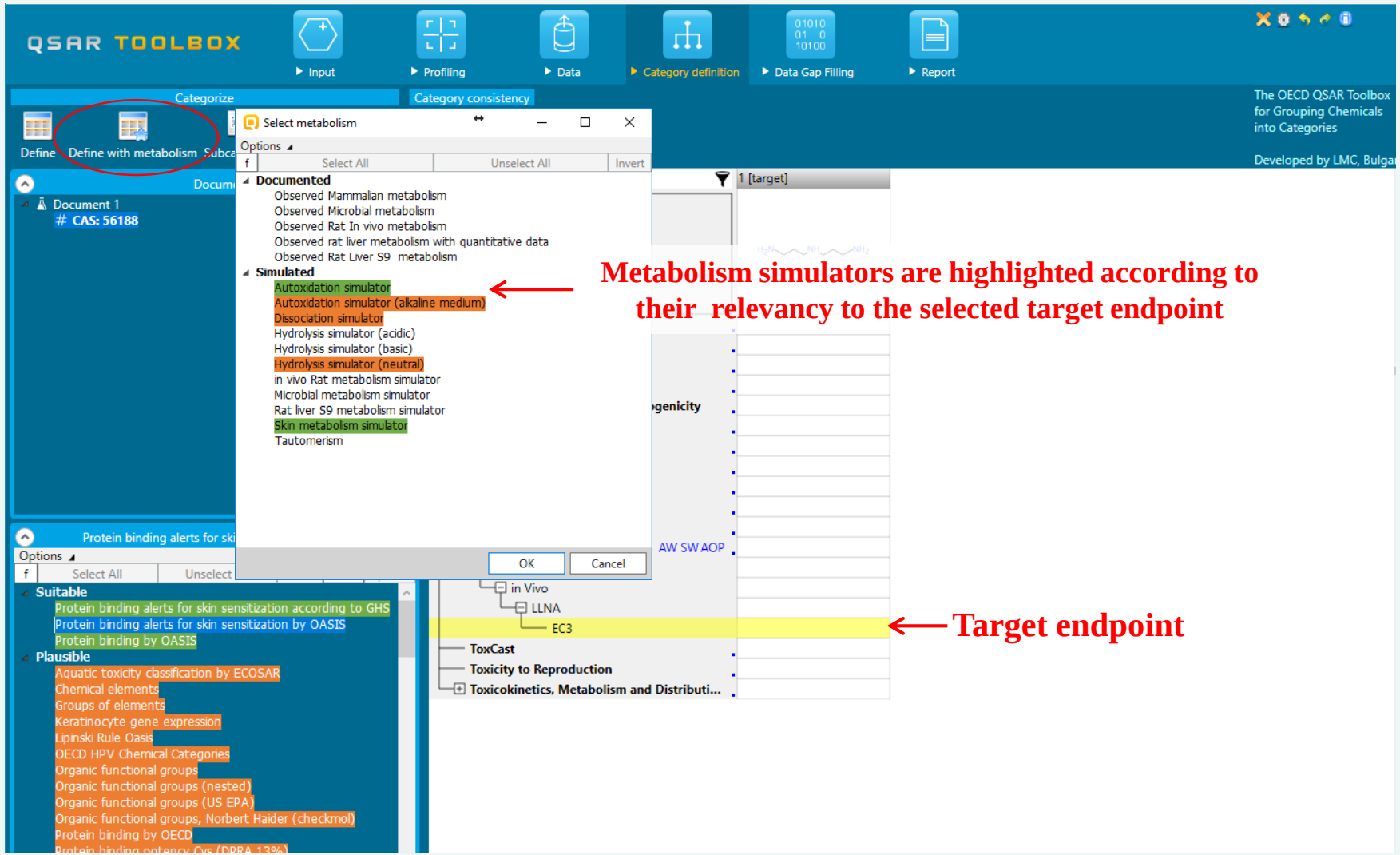
Category definition

Alert performance (AP) – with metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization



CAS 56-18-8



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Alert performance (AP) – with metabolic activation

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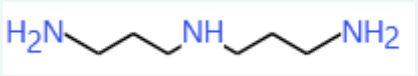

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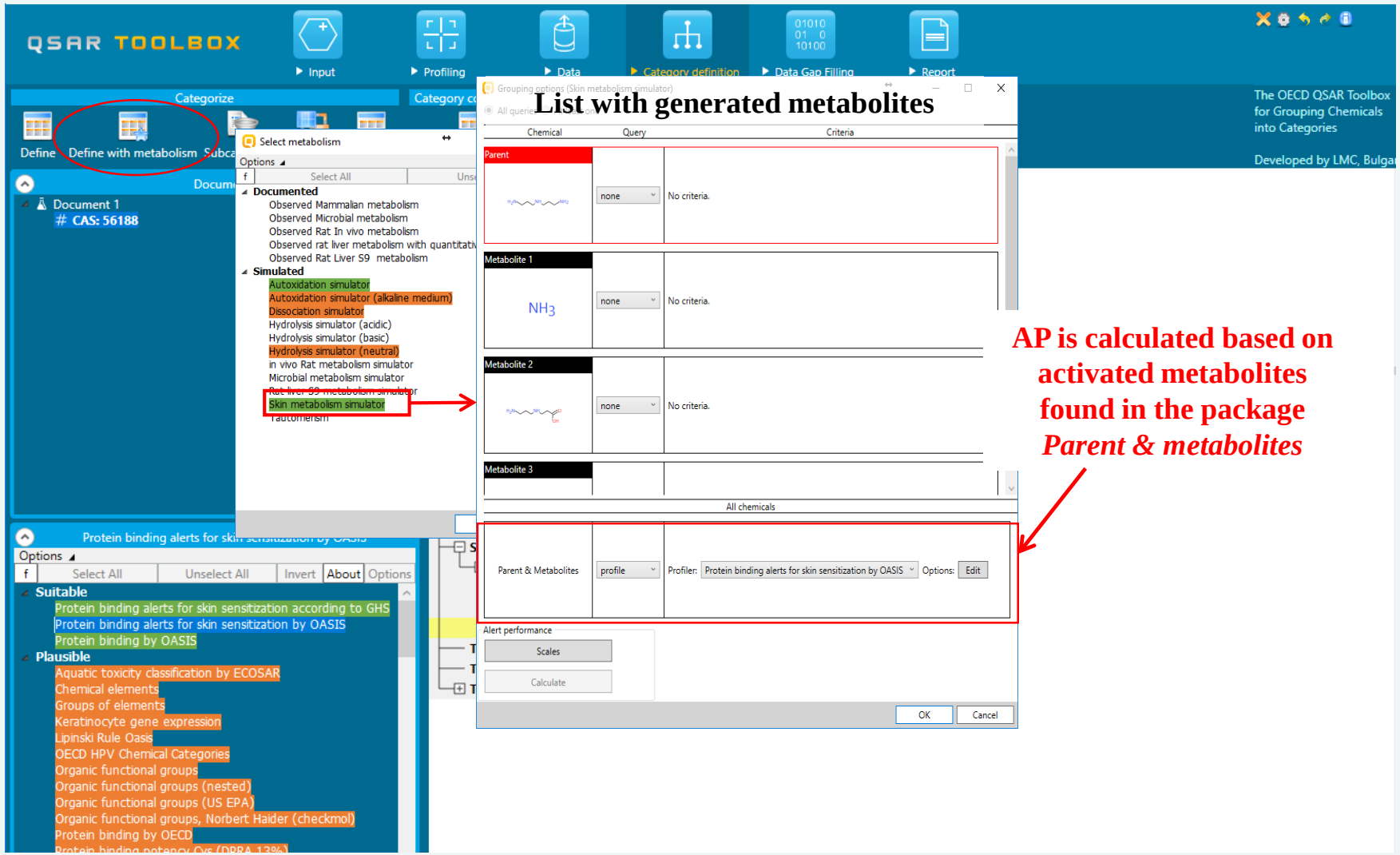

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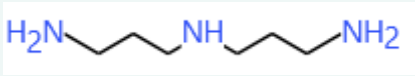

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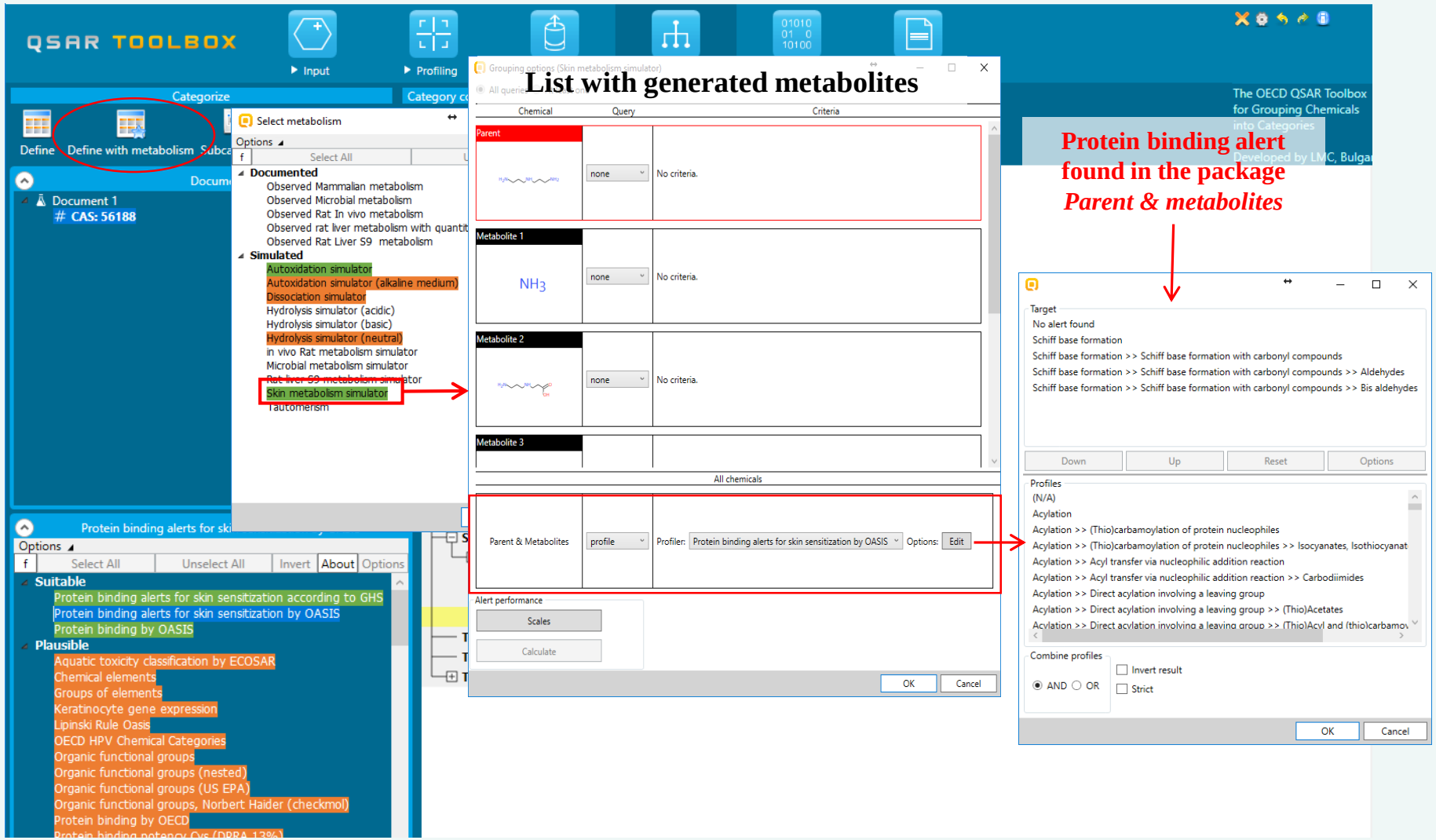

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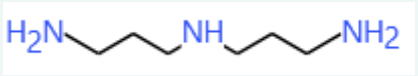

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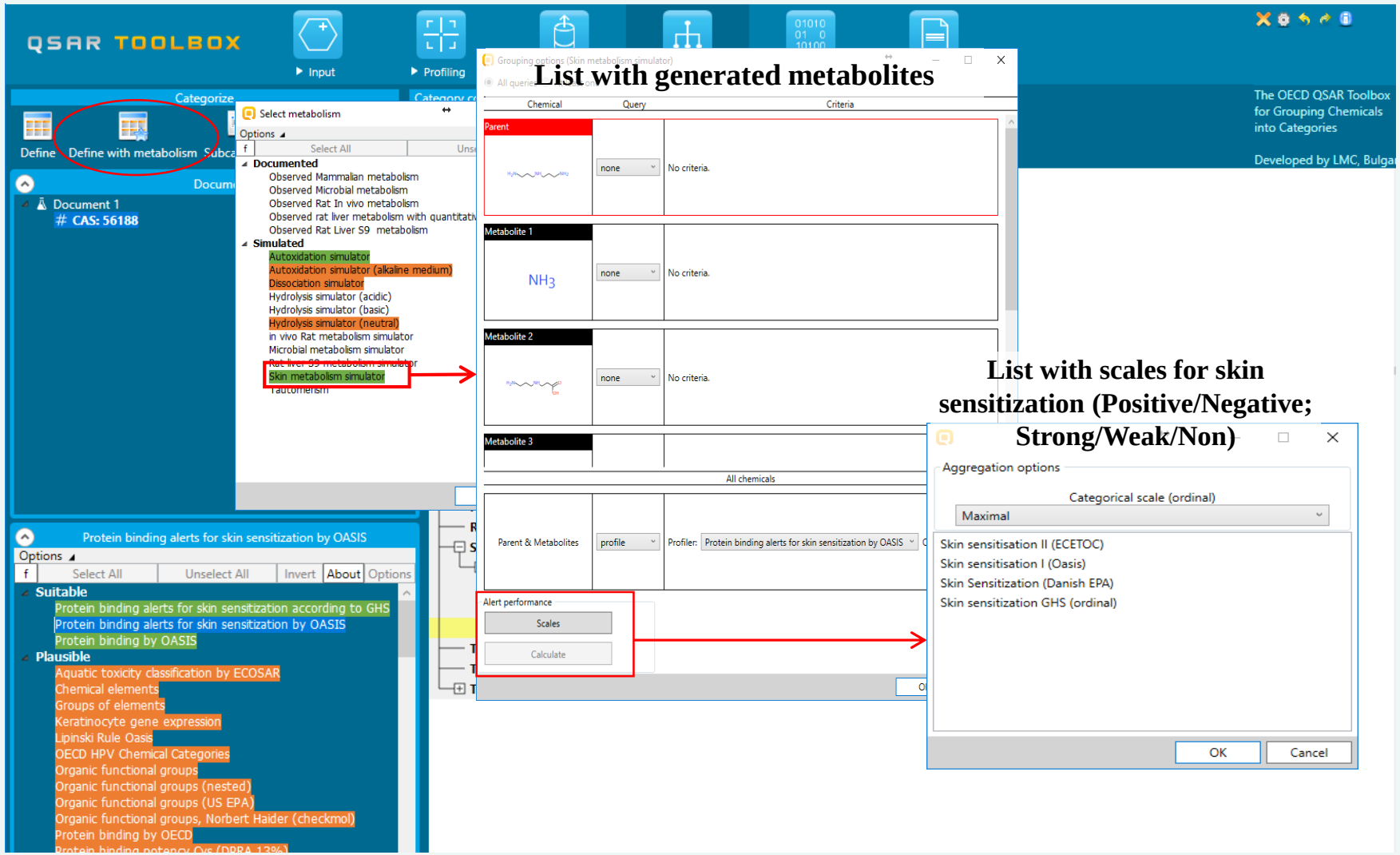

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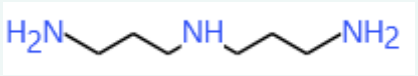

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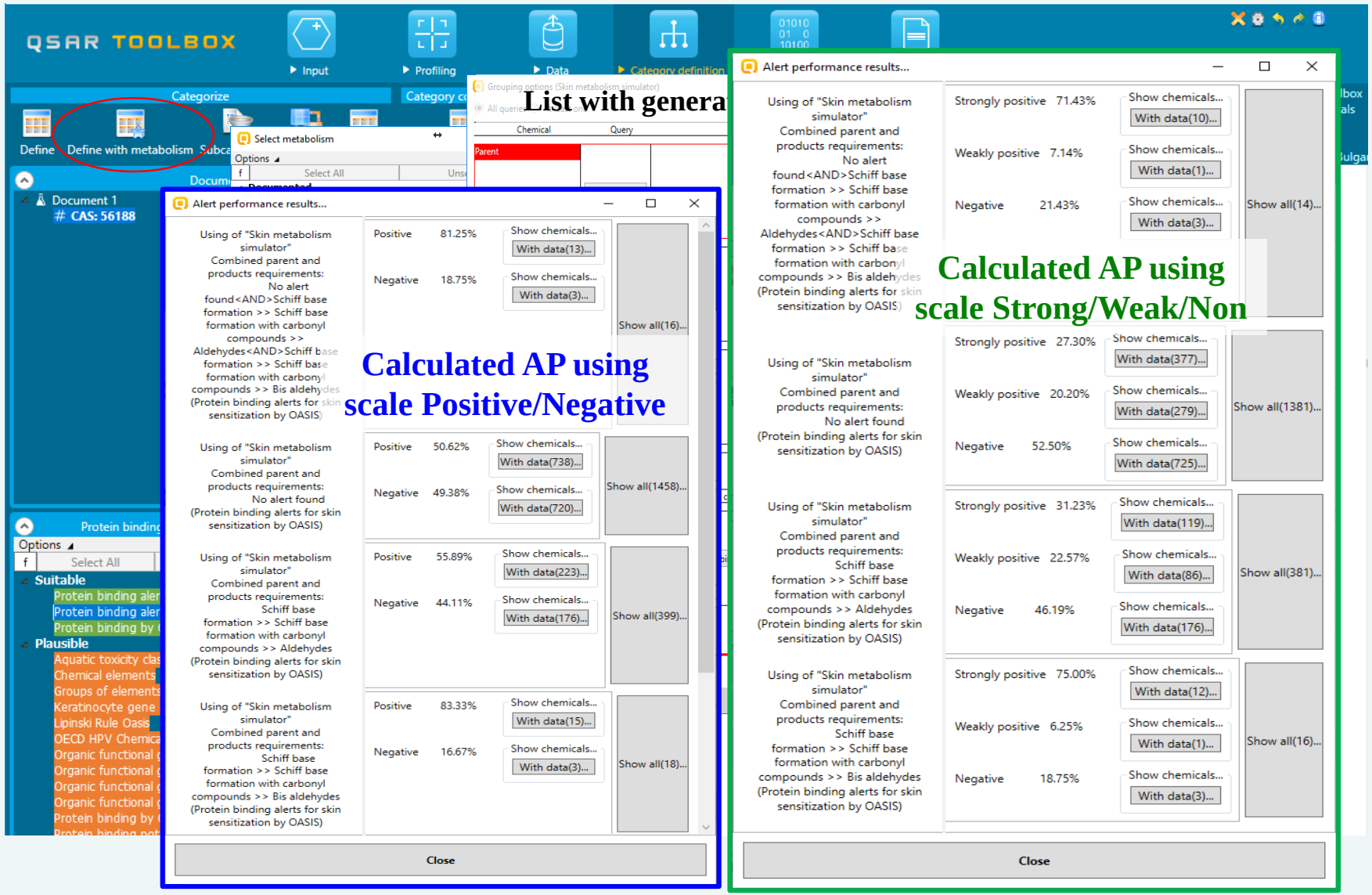

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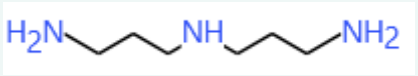

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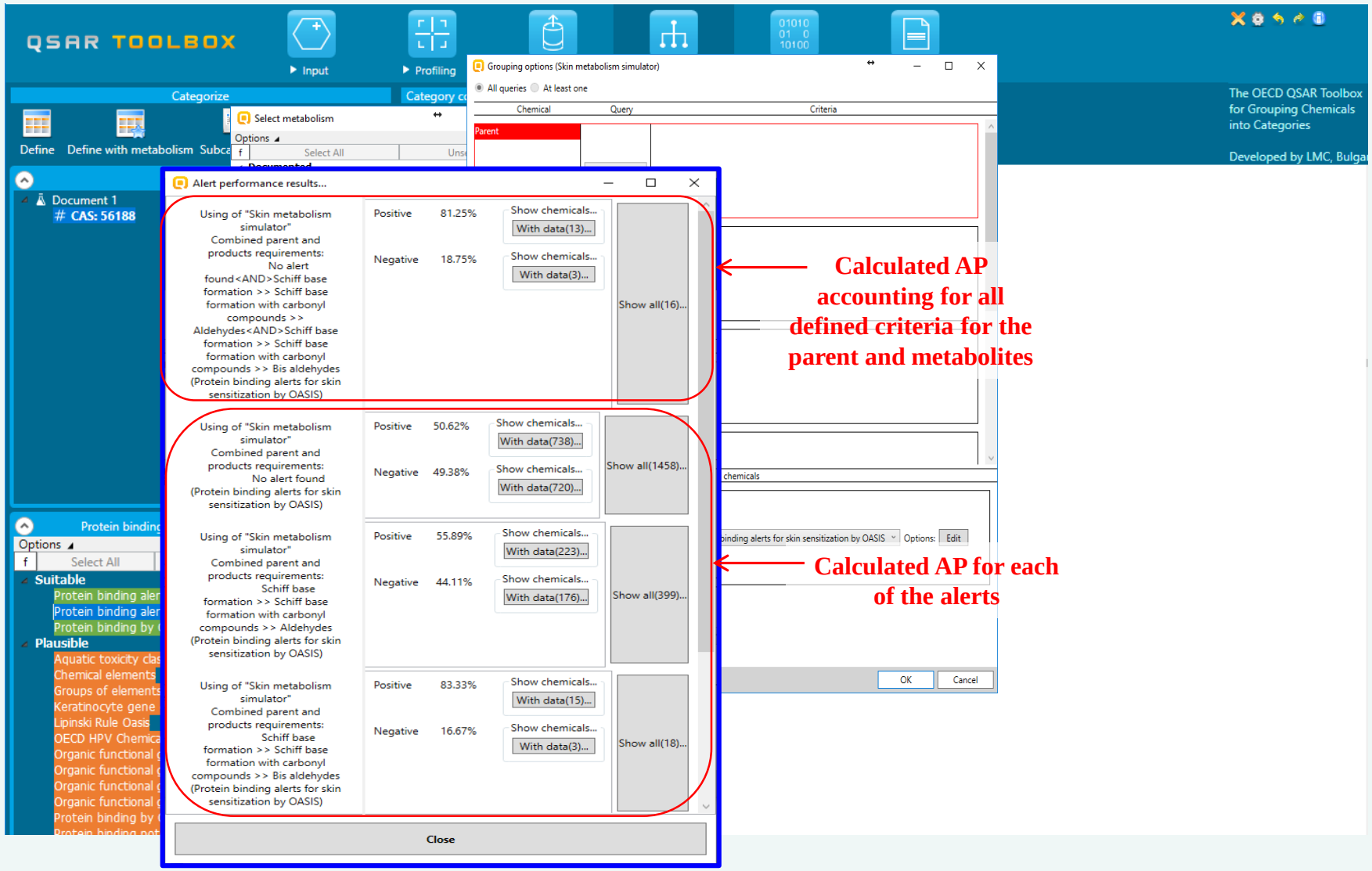

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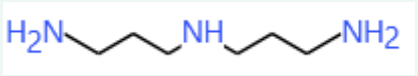

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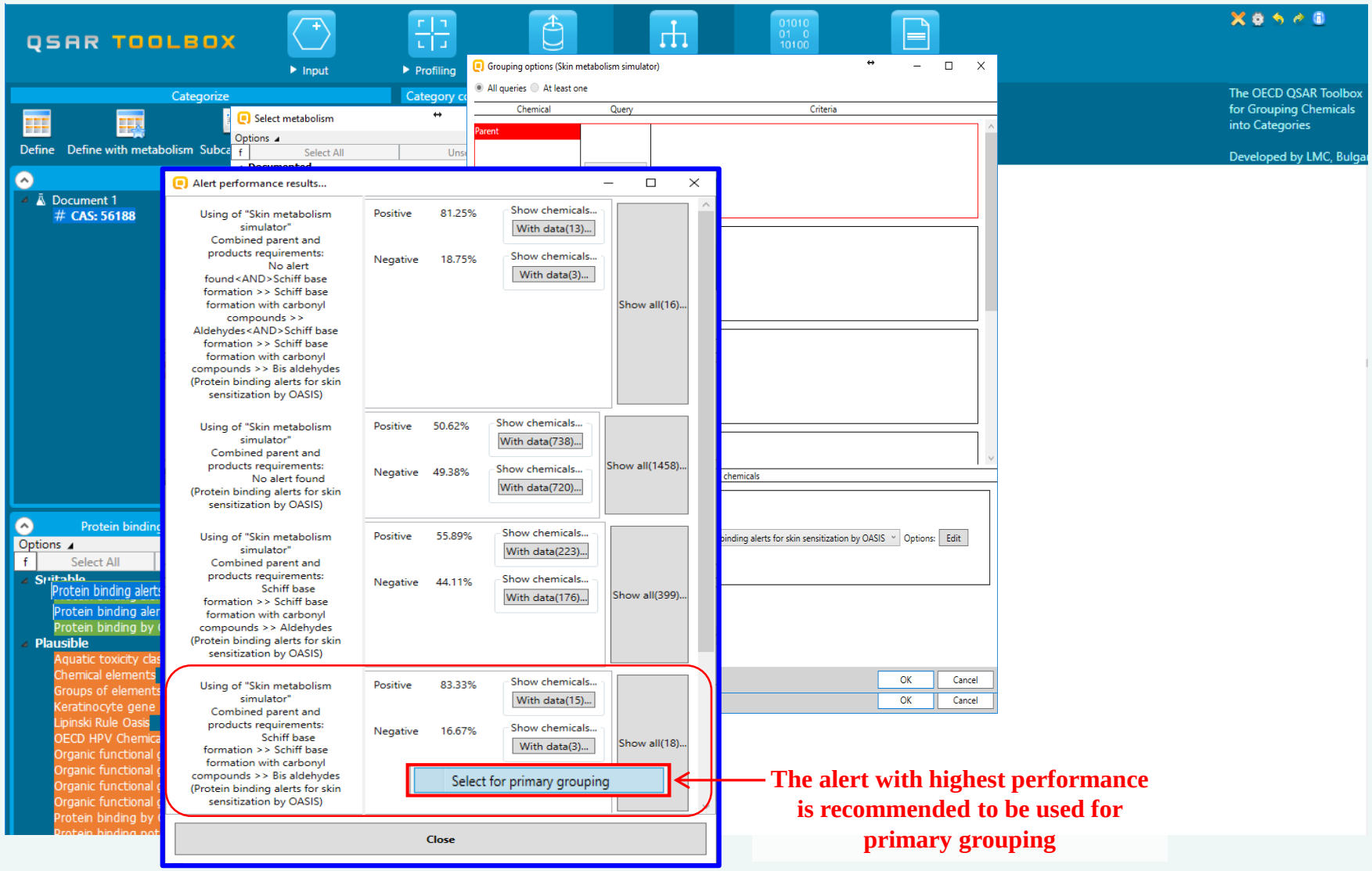

The alert with highest performance is recommended to be used for primary grouping

More information on Alert performance in Toolbox could be found in:

Yordanova, D., Schultz, T.W., Kuseva, C. Ivanova, H., Pavlov, T., Chankov, G., Karakolev, Y., Gissi, A., Sobanski, T. and Mekenyan, O.G. 2019. Alert performance: A new functionality in the OECD QSAR Toolbox. Comput. Toxicol. 10: 26-37.

List with tutorials:

- Tutorial on how to predict Skin sensitization potential taking into account alert performance
- Evaluating alert performance accounting for a metabolism