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 by the relevant profilers (highlighted in green): Target chemical is profiled as “Activated aryl and heteroaryl compounds” by profiler “Protein binding alerts for skin sensitization by OASIS”

Alert performance of alert “Activated aryl and heteroaryl compounds” will be evaluated
Category definition
Alert performance (AP)

Example
Target chemical: CAS 3934-20-1
Target endpoint: in vivo Skin Sensitization, LLNA, EC3

Databases
The databases having experimental data for the target endpoint need to be selected (highlighted in green):
Category definition
Alert performance (AP)

Example
Target chemical: CAS 3934-20-1
Target endpoint: in vivo Skin Sensitization, LLNA, EC3
Category definition
Alert performance (AP)

Example
Target chemical: CAS 3934-20-1

Target endpoint: in vivo Skin Sensitization, LLNA, EC3

Positive performance of alert “Activated aryl and heteroaryl compounds” is 90.32% (28 of 31 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
Problems resolved by AP:

1) Is the alert a SAR?

Example: CAS 3934-20-1 – Protein binding alert for SS is identified
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 98011
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

Two alerts for SS are found
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
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

First of the alerts is more relevant to the endpoint
Right click to select it for primary grouping
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
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Alert performance (AP)

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:
Profiling result for MBB by the new (modified) DNA “Haloalkane” alert

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

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
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Alert performance (AP)

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

DNA binding alerts for AMES are already identified in the first chemical (MBB)
Category definition

Alert performance (AP) – without metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

Target endpoint needs to be preliminary defined

Relevancy of the profilers (suitable, plausible and unknown) to the selected target endpoint
Category definition
Alert performance (AP) – without metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

List with scales for skin sensitization (Positive/Negative; Strong/Weak/Non)

Target’s protein binding alert and mechanism associated with skin sensitization
Category definition

Alert performance (AP) – **without** metabolic activation

*Calculation of AP for protein binding alert associated to Skin sensitization*

List with scales for skin sensitization (Positive/Negative; Strong/Weak/Non)

Target’s protein binding alert and mechanism associated with skin sensitization

Calculated AP using scale Positive/Negative

Calculated AP using scale Strong/Weak/Non
Category definition

Alert performance (AP) – with metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

CAS 56-18-8

Metabolism simulators are highlighted according to their relevancy to the selected target endpoint

Target endpoint
Category definition

Alert performance (AP) – with metabolic activation

*Calculation of AP for protein binding alert associated to Skin sensitization*

AP is calculated based on activated metabolites found in the package

Parent & metabolites
Category definition

Alert performance (AP) – with metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

CAS 56-18-8
Category definition

Alert performance (AP) – with metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

CAS 56-18-8
Category definition
Alert performance (AP) – with metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

CAS 56-18-8

List with generated metabolites
List with scales for skin sensitization (Positive/Negative; Strong/Weak/Non)

Calculated AP using scale Positive/Negative

Calculated AP using scale Strong/Weak/Non
Category definition

Alert performance (AP) – with metabolic activation

**Calculation of AP for protein binding alert associated to Skin sensitization**

CAS 56-18-8
Category definition

Alert performance (AP) – with metabolic activation

Calculation of AP for protein binding alert associated to Skin sensitization

The alert with highest performance is recommended to be used for primary grouping.
More information on Alert performance in Toolbox could be found in:


List with tutorials:
• Tutorial on how to predict Skin sensitization potential taking into account alert performance
• Evaluating alert performance accounting for a metabolism