



# QSAR Toolbox functionalities. Alert performance.

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## Category definition

### Alert performance (AP)

#### Usability

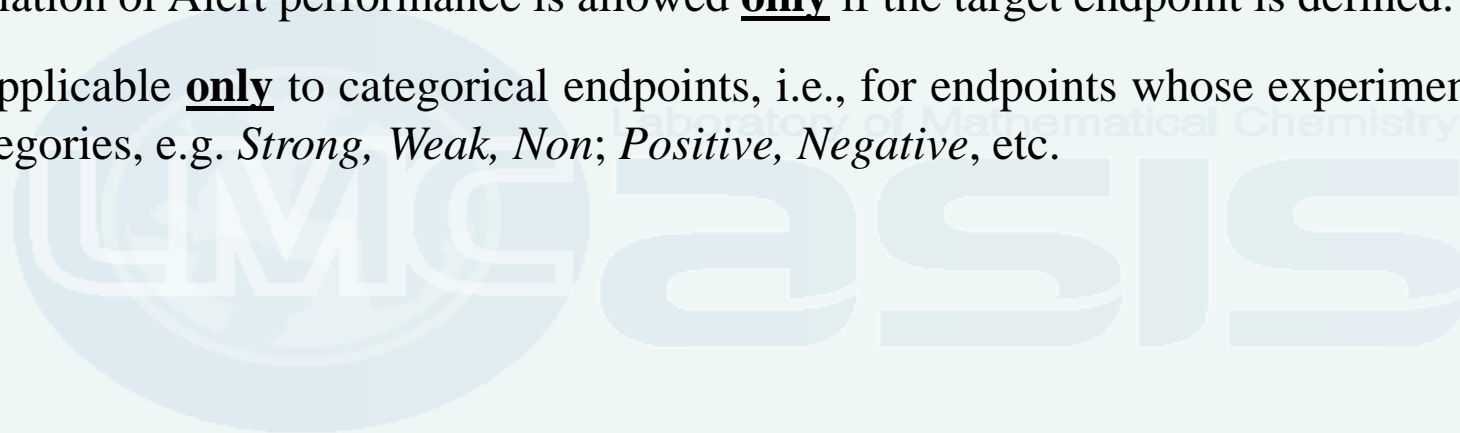
- Alert performance is used to define how much relevant to a target endpoint an alert is.
- Alert performance could be applied also to any profile categories; e.g., to organic functional group
- The reliability of alerts is context dependent and is significantly affected by target endpoint, selected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

Filter endpoint tree... 1 [target]

Structure

Human Health Hazards

- Acute Toxicity
- ADME
- Bioaccumulation
- Carcinogenicity
- Developmental Toxicity / Teratogenicity
- Genetic Toxicity
- Immunotoxicity
- Irritation / Corrosion
- Neurotoxicity
- Photoinduced toxicity
- Repeated Dose Toxicity
- Sensitisation AW SWAOP
  - Skin
  - in Vivo
    - LLNA
    - EC3
- ToxCast
- Toxicity to Reproduction
- Toxicokinetics, Metabolism and Distributi...

## Profiling results

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

QSAR TOOLBOX

Input Profiling Data Category definition Data Gap Filling

Profiling Custom profile

Apply View New Delete

Documents

- Document 1
  - # CAS: 66251
  - Aldehydes (Acute toxicity) (US-EPA New Chemical Ca
- Document 2
  - # CAS: 3934201

Filter endpoint tree... 1 [target]

Structure

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

Metabolism/Transformations

Options Select All Unselect All Invert

- Suitable
  - Autoxidation simulator
  - Skin metabolism simulator
- Plausible
  - Autoxidation simulator (alkaline medium)
  - Dissociation simulator
  - Hydrolysis simulator (neutral)

Protein binding by OASIS

Endpoint Specific

Protein binding alerts for skin sensitization by OASIS

SNAr

SNAr >> Nucleophilic aromatic substit...

SNAr >> Nucleophilic aromatic substit...

# Category definition

## Alert performance (AP)

Example

Target chemical: CAS 3934-20-1

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

## Databases

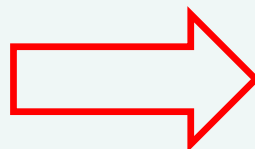
The databases having experimental data for the target endpoint need to be selected (highlighted in green):

Filter endpoint tree... 1 [target]

Structure

- Human Health Hazards
  - Acute Toxicity
  - ADME
  - Bioaccumulation
  - Carcinogenicity
  - Developmental Toxicity / Teratogenicity
  - Genetic Toxicity
  - Immunotoxicity
  - Irritation / Corrosion
  - Neurotoxicity
  - Photoinduced toxicity
  - Repeated Dose Toxicity
  - Sensitisation
    - Skin
      - in Vivo
      - LLNA
      - EC3
  - ToxCast
  - Toxicity to Reproduction
  - Toxicokinetics, Metabolism and Distributi...

AW SW AOP



QSAR TOOLBOX

Data Import Export Delete

Gather Import IUCLID6 IUCLID6 Database Inventory

Documents

- Document 1
  - # CAS: 66251
    - Aldehydes (Acute toxicity) (US-EPA New Chemical Ca
- Document 2
  - # CAS: 3934201

Databases

Options

- Select All Unselect All Invert
- Data available
  - ECHA CHEM
  - REACH Skin sensitisation database (normalised)
  - Skin Sensitization
- No data available
  - Acute Oral toxicity DB
  - ADME Database
  - Aquatic ECETOC
  - Aquatic Japan MoE
  - Aquatic OASIS
  - Bacterial mutagenicity ISSSTY
  - Bioaccumulation Canada
  - Bioaccumulation fish CEFIC LRI

Inventories

Filter endpoint tree... 1 [target]

Structure

- Human Health Hazards
  - Acute Toxicity
  - ADME
  - Bioaccumulation
  - Carcinogenicity
  - Developmental Toxicity / Teratogenicity
  - Genetic Toxicity
  - Immunotoxicity
  - Irritation / Corrosion
  - Neurotoxicity
  - Photoinduced toxicity
  - Repeated Dose Toxicity
  - Sensitisation
    - Skin
      - in Vivo
      - LLNA
      - EC3
  - ToxCast
  - Toxicity to Reproduction
  - Toxicokinetics, Metabolism and Distri...

AW SW AOP

# Category definition

## Alert performance (AP)

Example

Target chemical: CAS 3934-20-1

Target endpoint: in vivo Skin Sensitization, LLNA, EC3

Click "Define"

Select "Protein binding alerts for skin sensitization by OASIS" profiler

Click "Scales"

Select "Skin sensitization II (ECETOC)" scale and press "OK"

Calculate:

# Category definition

## Alert performance (AP)

### Example

Target chemical: CAS 3934-20-1

Target endpoint: in vivo Skin Sensitization, LLNA, EC3

The screenshot displays the QSAR Toolbox software interface. The top navigation bar includes 'Input', 'Profiling', 'Data', 'Category definition' (highlighted with a red box), 'Data Gap Filling', and 'Report'. The left sidebar shows a document list with 'Document 1' selected, containing chemical information: '# [C: 1;Md: 0;P: 0] CAS: 3934201'. Below this, a list of protein binding alerts for skin sensitization by OASIS is shown, with 'Suitable' and 'Plausible' categories expanded. The main workspace displays a 'Filter endpoint tree...' with a hierarchical structure of toxicity endpoints. The 'Sensitisation' endpoint is expanded to show 'Skin' and 'in Vivo' sub-endpoints, with 'LLNA' and 'EC3' selected. An 'Alert performance results...' dialog box is overlaid on the right, showing the performance of an SNAr alert: 'SNAr >> Nucleophilic aromatic substitution on activated aryl and heteroaryl compounds >> Activated aryl and heteroaryl compounds'. The dialog displays a table of results:

Category	Percentage	Action
Positive	90.63%	Show chemicals... With data(29)...
Negative	9.38%	Show chemicals... With data(3)...

The dialog also includes a 'Show all(32)...' button and a 'Close' button at the bottom.

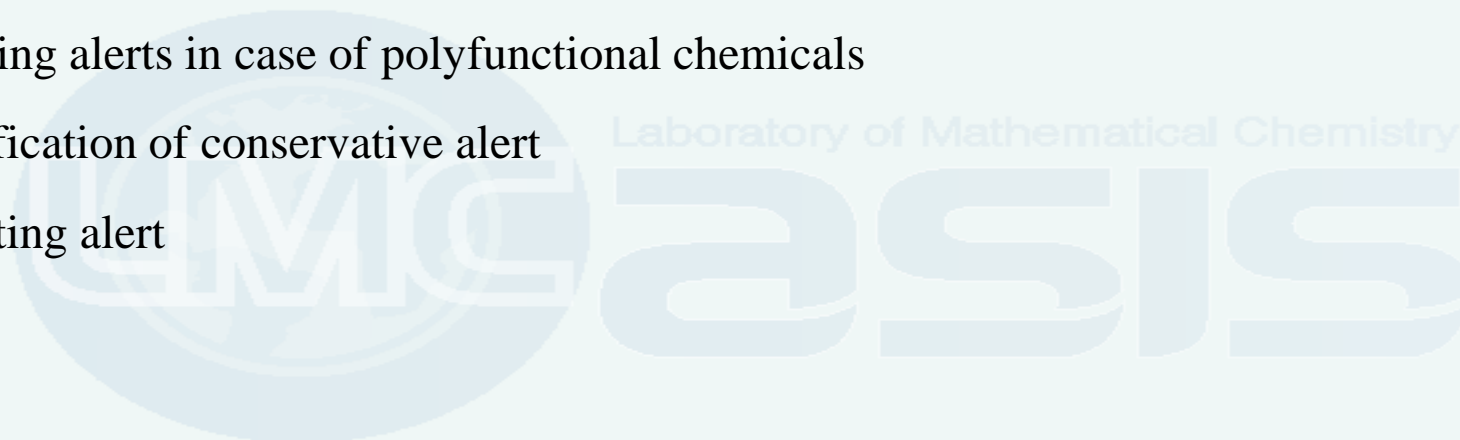
Positive performance of alert “*Activated aryl and heteroaryl compounds*” is **90.63%** (29 out of 32 chemicals having this alert are positive skin sensitizers)

## 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

The screenshot displays a software interface for chemical safety. At the top, there is a search bar with the text "Filter endpoint tree..." and a dropdown menu showing "1 [target]". Below this is a "Structure" section containing a chemical structure of 2,6-dichloropyridine, represented by a pyridine ring with chlorine atoms at the 2 and 6 positions. To the left of the main content is a tree view of hazard categories. The "Sensitisation" category is expanded, showing sub-categories: "Skin", "in Vivo", and "LLNA". The "LLNA" category is further expanded to show "EC3", which is highlighted in yellow. Below the tree view, there is a red-bordered box containing the following text:

Protein binding alerts for skin sensitization by OASIS  
SNAr  
SNAr >> Nucleophilic aromatic substitution on activated aryl and heteroaryl compounds  
SNAr >> Nucleophilic aromatic substitution on activated aryl and heteroaryl compounds >> Activated aryl and heteroaryl compounds

# 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

The screenshot displays a software interface for chemical analysis. On the left, a 'Filter endpoint tree...' shows a hierarchical list of categories under 'Human Health Hazards', with 'Sensitisation' and 'EC3' highlighted. The main area shows the chemical structure of 2,6-dichloropyridine. Overlaid on this are two windows: 'Grouping options (Protein binding alerts for skin sensitization by OASIS)' and 'Alert performance results...'. The 'Alert performance results...' window contains a table with the following data:

Category	Positive	Negative
SNAr >> Nucleophilic aromatic substitution on activated aryl and heteroaryl compounds >> Activated aryl and heteroaryl compounds	90.63%	9.38%

Buttons for 'Show chemicals... With data(29)...' and 'Show chemicals... With data(3)...' are visible next to the respective rows. A 'Show all(32)...' button is also present. The interface includes 'Options' for 'Combine profiles' (AND/OR) and 'Alert performance' (Scales/Calculate). At the bottom, there are 'OK' and 'Cancel' buttons.

# 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

Filter endpoint tree... 1 [target]

Structure

O=Cc1ccoc1

Endpoint	Count	Metric	Result
Human Health Hazards			
Acute Toxicity			
Bioaccumulation			
Carcinogenicity			
Developmental Toxicity / Teratogenicity			
Genetic Toxicity			
in Vitro			
Chromosome aberration	1/3	M: Negative	
Gene mutation			
Bacterial Reverse Mutation Assay (...)			
Salmonella typhimurium			
No S9 Info	1/1	M: Positive	
With S9	1/14	M: Negative	
Without S9	1/13	M: Negative	
Mammalian Cell Gene Mutatio...	1/1	M: Positive	
Immunotoxicity			
Irritation / Corrosion			
Neurotoxicity			
Photoinduced toxicity			
Repeated Dose Toxicity			
Sensitisation			
ToxCast			
Toxicity to Reproduction			
Toxicokinetics, Metabolism and Distributi...			
Profile			
General Mechanistic			
DNA binding by OASIS		No alert found	
DNA binding by OECD			

Michael addition  
Michael addition >> P450 Mediated Activation of Heterocyclic Ring Systems  
Michael addition >> P450 Mediated Activation of Heterocyclic Ring Systems >> Furans

# 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

The screenshot displays a software interface for chemical analysis. On the left is a 'Filter endpoint tree...' with a hierarchical list of categories. The 'DNA binding by OECD' category is selected. In the center, a chemical structure of furfural is shown. Two dialog boxes are overlaid on the interface:

- Grouping options (DNA binding by OECD)**: Shows target categories and options for grouping.
- Alert performance results...**: Shows a table of alert performance results. The 'Negative' row is highlighted with a red box.

Category	Percentage	Show chemicals... With data...
Michael addition	14.63%	With data(6)...
Michael addition >> P450 Mediated Activation of Heterocyclic Ring Systems	0.00%	With data(0)...
Michael addition >> P450 Mediated Activation of Heterocyclic Ring Systems >> Furans	85.37%	With data(35)...

At the bottom of the interface, the following text is displayed:

No alert found  
Michael addition  
Michael addition >> P450 Mediated Activation of Heterocyclic Ring Systems  
Michael addition >> P450 Mediated Activation of Heterocyclic Ring Systems >> Furans

# 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

Filter endpoint tree... 1 [target]

Structure

Sensitisation AW SWAOP

- Skin
  - in Vivo
    - LLNA
      - EC3

ToxCast

Toxicity to Reproduction

Toxicokinetics, Metabolism and Distributi...

Profile

- Endpoint Specific
  - Protein binding alerts for skin sensitization by OASIS

Acylation

- Acylation >> Direct acylation involving a leaving group
- Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio)carbamoyl halides and cyanides
- Acylation >> Ester aminolysis or thiolysis
- Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters

**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

The screenshot displays a software interface for filtering endpoints and viewing alert performance results. On the left, a 'Filter endpoint tree...' window shows a hierarchical tree of endpoints. The 'EC3' endpoint under 'Sensitisation' is highlighted in yellow. Below it, 'Protein binding alerts for skin sensitization by OASIS' is listed. In the center, a 'Grouping options' window is open, showing target categories for 'Protein binding alerts for skin sensitization by OASIS'. The categories listed are 'Acylation', 'Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio) carbamoyl halides and cyanides <AND> Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters', and 'Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters'. On the right, an 'Alert performance results...' window is open, showing a table of results for the selected categories. A blue box highlights the first category, which has no data. A blue arrow points to this box with the text 'No chemicals having both alerts are found'. The table below shows performance metrics for other categories.

Category	Positive	Negative	With data
Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio) carbamoyl halides and cyanides <AND> Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters	84.62%	15.38%	11
Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio) carbamoyl halides and cyanides	66.67%	33.33%	8
Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters	33.33%	66.67%	4

# 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**

The screenshot displays a software interface for managing alerts. On the left, a 'Filter endpoint tree...' shows a hierarchy of categories including 'Sensitisation', 'ToxCast', and 'Profile'. The 'EC3' endpoint is highlighted in yellow. In the center, a 'Grouping options (Protein binding alerts for skin sensitization by OASIS)' dialog is open, listing target categories such as 'Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio) carbamoyl halides and cyanides<AND>Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters'. On the right, an 'Alert performance results...' dialog is open, showing a table of alert performance data. The first alert category has a positive performance of 84.62% and a negative performance of 33.33%. A red box highlights the 'Select for primary grouping' button for the first alert category. A green arrow points to the first alert category in the table, and a red arrow points to the 'Select for primary grouping' button. Text annotations in green and red provide instructions: 'First of the alerts is more relevant to the endpoint' and 'Right click to select it for primary grouping'.

Alert Category	Positive	Negative
Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio) carbamoyl halides and cyanides<AND>Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters	84.62%	33.33%
Acylation >> Ester aminolysis or thiolysis >> Activated (di)aryl esters		

# Category definition

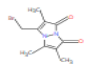

## Alert performance (AP)

### Problems resolved by AP:

#### 4) Adjusting alert boundaries

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

The screenshot displays a software interface for chemical alert performance. On the left, a sidebar contains a tree view with categories: Structure info, Parameters, Physical Chemical Properties, Environmental Fate and Transport, Ecotoxicological Information, Human Health Hazards, and Profiling. Under Profiling, there are sub-categories: DNA binding by OASIS, DNA binding by OECD, Endpoint Specific, and DNA alerts for AMES by OASIS. The main area is a table with two columns, labeled 2 and 3. Column 2 contains a chemical structure of a highly reactive compound. Column 3 contains a chemical structure of a less reactive compound. A green box highlights the two structures, with a green arrow pointing to a text box that reads "Two highly reactive chemicals toward proteins". A red box highlights the alert lists for both structures, with a red arrow pointing to a text box that reads "No DNA binding alerts for AMES are identified in the first chemical (MBB)". The alert list for the first chemical (column 2) shows "No alert found". The alert list for the second chemical (column 3) shows several alerts, including AN2 (Shiff base formation for aldehydes) and SN2 (Acylation involving a leaving group, Alkylation, nucleophilic substitution at sp3-carbon atom, DNA alkylation, and Internal SN2 reaction with aziridinium and/or cyclic sulfonium ion formation).

2	3
	
No alert found	AN2 AN2 >> Shiff base formation for aldehydes AN2 >> Shiff base formation for aldehydes >> Haloalkane Derivatives with Labile Halogen SN2 SN2 >> Acylation involving a leaving group SN2 >> Acylation involving a leaving group >> Haloalkane Derivatives with Labile Halogen SN2 >> Alkylation, nucleophilic substitution at sp3-carbon atom SN2 >> Alkylation, nucleophilic substitution at sp3-carbon atom >> Haloalkane Derivatives with L SN2 >> DNA alkylation SN2 >> DNA alkylation >> Vicinal Dihaloalkanes SN2 >> Internal SN2 reaction with aziridinium and/or cyclic sulfonium ion formation (enzymatic) SN2 >> Internal SN2 reaction with aziridinium and/or cyclic sulfonium ion formation (enzymatic) >
No alert found	No alert found
No alert found	AN2 AN2 >> Shiff base formation for aldehydes AN2 >> Shiff base formation for aldehydes >> Haloalkane Derivatives with Labile Halogen SN2 SN2 >> Acylation involving a leaving group SN2 >> Acylation involving a leaving group >> Haloalkane Derivatives with Labile Halogen SN2 >> Alkylation, nucleophilic substitution at sp3-carbon atom SN2 >> Alkylation, nucleophilic substitution at sp3-carbon atom >> Haloalkane Derivatives with L



# Category definition

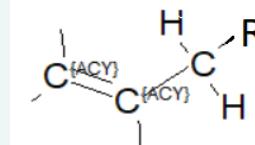
## Alert performance (AP)

### 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**

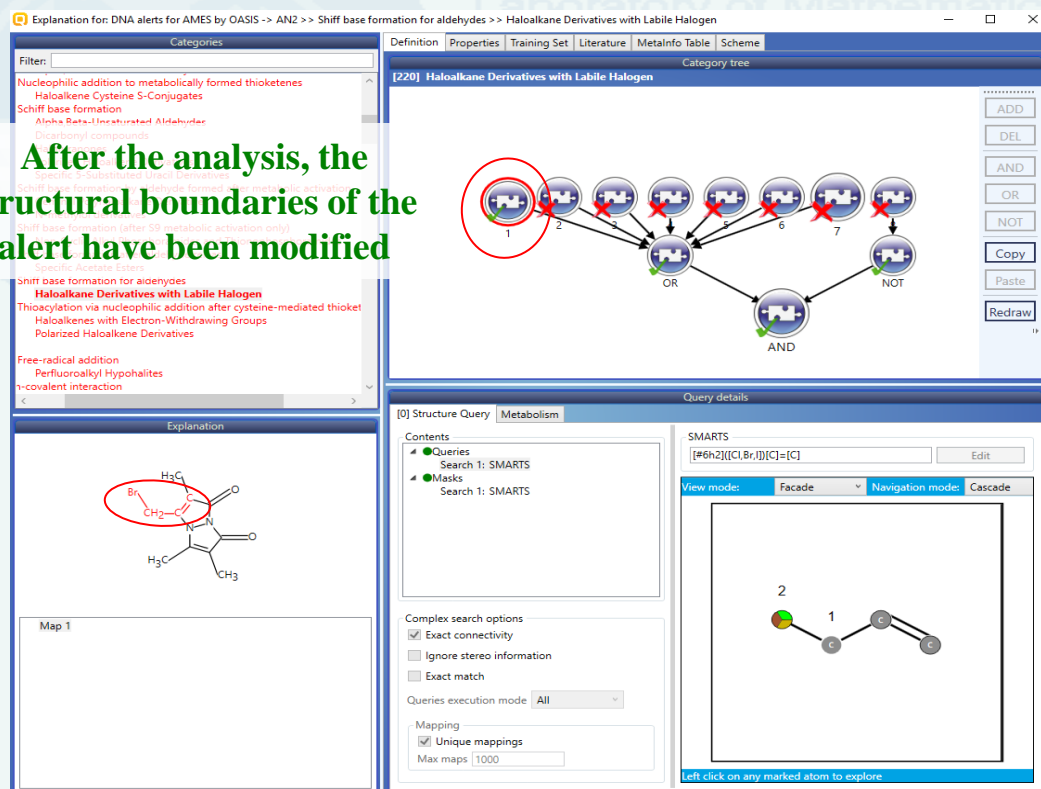
Original structural boundary of DNA  
“Haloalkane” alert



R = Cl, Br, I

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

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



Explanation for: DNA alerts for AMES by OASIS -> AN2 >> Schiff base formation for aldehydes >> Haloalkane Derivatives with Labile Halogen

Categories

Filter:

- Nucleophilic addition to metabolically formed thioketenes
- Haloalkane Cysteine S-Conjugates
- Schiff base formation
- Alkyls Beta-unsaturated Aldehydes
- Acetyl compounds
- Schiff base formation for aldehyde formed by metabolic activation
- Schiff base formation after S-metabolic activation
- Specific Acetate Esters
- Schiff base formation for aldehydes
- Haloalkane Derivatives with Labile Halogen
- Thioacylation via nucleophilic addition after cysteine-mediated thio
- Haloalkenes with Electron-Withdrawing Groups
- Polarized Haloalkene Derivatives
- Free-radical addition
- Perfluoroalkyl Hypohalites
- π-covalent interaction

Definition | Properties | Training Set | Literature | MetaInfo Table | Scheme

[220] Haloalkane Derivatives with Labile Halogen

Category tree

ADD  
DEL  
AND  
OR  
NOT  
Copy  
Paste  
Redraw

[0] Structure Query | Metabolism

Contents

- Queries  
Search 1: SMARTS
- Masks  
Search 1: SMARTS

Complex search options

- Exact connectivity
- Ignore stereo information
- Exact match

Queries execution mode: All

Mapping

- Unique mappings
- Max maps: 1000

SMARTS

[\*]6h2([C],Br,I)[C]=[C]

View mode: Facade | Navigation mode: Cascade

Left click on any marked atom to explore

# Category definition

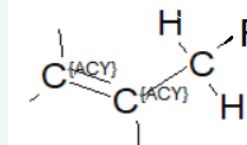
## Alert performance (AP)

### 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**

Original structural boundary of DNA  
“Haloalkane” alert



R = Cl, Br, I

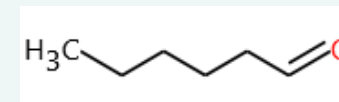
### Profiling result for MBB by the DNA alerts for AMES by OASIS

The screenshot shows the OASIS software interface. On the left, there is a sidebar with a tree view containing categories like 'Structure info', 'Parameters', 'Physical Chemical Properties', 'Environmental Fate and Transport', 'Ecotoxicological Information', 'Human Health Hazards', 'Profile', 'General Mechanistic', 'DNA binding by OASIS', 'DNA binding by OECD', 'Endpoint Specific', and 'DNA alerts for AMES by OASIS'. The main area is divided into two columns, labeled '1 [target]' and '2'. Each column shows a chemical structure and a list of alerts. A red box highlights the alert list for target 1, and a red arrow points to the text 'DNA binding alerts for AMES are already identified in the first chemical (MBB)'. The alert list for target 1 includes: AN2, AN2 >> Schiff base formation for aldehydes, AN2 >> Schiff base formation for aldehydes >> Haloalkane Derivatives with Labile Halogen, SN2, SN2 >> Acylation involving a leaving group, SN2 >> Acylation involving a leaving group >> Haloalkane Derivatives with Labile Halogen, and SN2 >> Alkylation, nucleophilic substitution at sp3-carbon atom. The alert list for target 2 is identical but ends with 'Haloalkane Derivatives wi...'. The text 'No alert found' is displayed below the alert lists for both targets.

# Category definition

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

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



CAS 66-25-1

The screenshot displays the QSAR Toolbox interface. The 'Category definition' tab is active, and the 'Filter endpoint tree...' window is open. The tree structure shows the following endpoints:

- Human Health Hazards
  - Acute Toxicity
  - ADME
  - Bioaccumulation
  - Carcinogenicity
  - Developmental Toxicity / Teratogenicity
  - Genetic Toxicity
  - Immunotoxicity
  - Irritation / Corrosion
  - Neurotoxicity
  - Photoinduced toxicity
  - Repeated Dose Toxicity
  - Sensitisation (AW SW AOP)
    - Skin
    - in Vivo
    - LLNA
    - EC3
  - ToxCast
  - Toxicity to Reproduction
  - Toxicokinetics, Metabolism and Distribution

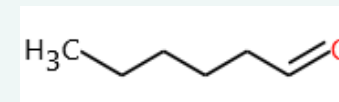
The 'EC3' endpoint is highlighted in yellow. A red box highlights the 'Sensitisation' endpoint and its sub-endpoints. A red arrow points from the 'Sensitisation' endpoint to a red text box that reads: "Relevancy of the profilers (suitable, plausible and unknown) to the selected target endpoint".

The 'Documents' panel on the left shows a document with CAS: 66251. The 'Protein binding alerts for skin sensitization by OASIS' panel is also visible, showing a list of alerts categorized as 'Suitable' or 'Plausible'.

# Category definition

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

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



CAS 66-25-1

The screenshot displays the QSAR Toolbox software interface with several key components highlighted:

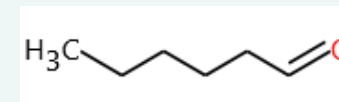
- Target's protein binding alert and mechanism associated with skin sensitization:** A red box highlights the "Target categories" section in the "Grouping options" dialog, listing "Schiff base formation" and its associated mechanisms: "Schiff base formation >> Schiff base formation with carbonyl compounds" and "Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes".
- Alert performance section:** A red box highlights the "Alert performance" section in the "Grouping options" dialog, showing the "Scales" and "Calculate" buttons.
- List with scales for skin sensitization (Positive/Negative; Strong/Weak/Non):** A separate dialog box titled "Aggregation options" shows a list of scales for skin sensitization, including "Skin sensitisation II (ECETOC)", "Skin sensitisation I (Oasis)", "Skin Sensitization (Danish EPA)", and "Skin sensitization GHS (ordinal)".

The background interface shows the "Define" menu, "Protein binding alerts for skin sensitization" options, and a tree view of chemical categories.

# Category definition

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

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



CAS 66-25-1

**Target's protein binding alert and mechanism associated with skin sensitization**

**Alert performance section**

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

**Calculated AP using scale Positive/Negative**

**Calculated AP using scale Strong/Weak/Non**

Alert	Positive	Negative
Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes	84.06%	15.94%

Alert	Strongly positive	Weakly positive	Negative
Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes	29.41%	54.41%	16.18%

# Category definition

Alert performance (AP) – **with** metabolic activation

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



CAS 56-18-8

The screenshot displays the QSAR TOOLBOX interface. The 'Select metabolism' dialog box is open, showing a list of metabolism simulators. The 'Simulated' section includes: Autoxidation simulator, Autoxidation simulator (alkaline medium), Dissociation simulator, Hydrolysis simulator (acidic), Hydrolysis simulator (basic), Hydrolysis simulator (neutral), in vivo Rat metabolism simulator, Microbial metabolism simulator, Rat liver S9 metabolism simulator, Skin metabolism simulator, and Tautomerism. The 'Autoxidation simulator (alkaline medium)' is highlighted in orange, and the 'Skin metabolism simulator' is highlighted in green. A red arrow points to the orange highlight. The 'in Vivo' section includes LLNA and EC3, with EC3 highlighted in yellow and a red arrow pointing to it. The background shows a tree view of categories and a target endpoint list.

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*



CAS 56-18-8

**List with generated metabolites**

Chemical	Query	Criteria
Parent	<chem>NCCCCNC(C)CCN</chem>	none No criteria.
Metabolite 1	NH <sub>3</sub>	none No criteria.
Metabolite 2	<chem>NCCCCNC(C)CCN</chem>	none No criteria.
Metabolite 3		

Alert performance

Parent & Metabolites	profile	Profiler: Protein binding alerts for skin sensitization by OASIS Options: Edit
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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

**Protein binding alert found in the package Parent & metabolites**

Chemical	Query	Criteria
	none	No criteria.
NH <sub>3</sub>	none	No criteria.
	none	No criteria.
	none	No criteria.

Alert performance

Parent & Metabolites profile Profile: Protein binding alerts for skin sensitization by OASIS Options: Edit

Target

No alert found

Schiff base formation

Schiff base formation >> Schiff base formation with carbonyl compounds

Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes

Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes

Profiles

(N/A)

Acylation

Acylation >> (Thio)carbamoylation of protein nucleophiles

Acylation >> (Thio)carbamoylation of protein nucleophiles >> Isocyanates, Isothiocyanat

Acylation >> Acyl transfer via nucleophilic addition reaction

Acylation >> Acyl transfer via nucleophilic addition reaction >> Carbodiimides

Acylation >> Direct acylation involving a leaving group

Acylation >> Direct acylation involving a leaving group >> (Thio)Acetates

Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio)carbamoylation

Combine profiles

AND  OR  Invert result  Strict

# Category definition

Alert performance (AP) – **with** metabolic activation

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



CAS 56-18-8

The screenshot displays the QSAR TOOLBOX interface. On the left, the 'Categorize' panel shows a document for CAS: 56188. The 'Select metabolism' dialog is open, listing various simulators. The 'Skin metabolism simulator' is highlighted with a red box and an arrow pointing to the 'List with generated metabolites' window. This window shows a table with columns for Chemical, Query, and Criteria. The 'Parent' row shows the chemical structure and 'none' for both Query and Criteria. The 'Metabolite 1' row shows the chemical structure NH<sub>3</sub> and 'none' for both. The 'Metabolite 2' row shows a chemical structure with a red 'S' atom and 'none' for both. The 'Metabolite 3' row is empty. Below this, the 'Alert performance' dialog is open, showing 'Scales' and 'Calculate' buttons. A red arrow points from the 'Calculate' button to the 'List with scales for skin sensitization (Positive/Negative; Strong/Weak/Non)' dialog. This dialog shows 'Aggregation options' with 'Maximal' selected and a list of scales: Skin sensitisation II (ECETOC), Skin sensitisation I (Oasis), Skin Sensitization (Danish EPA), and Skin sensitization GHS (ordinal).

Chemical	Query	Criteria
	none	No criteria.
NH <sub>3</sub>	none	No criteria.
	none	No criteria.

Alert performance

Scales

Calculate

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

Aggregation options

Maximal

Categorical scale (ordinal)

- Skin sensitisation II (ECETOC)
- Skin sensitisation I (Oasis)
- Skin Sensitization (Danish EPA)
- Skin sensitization GHS (ordinal)

# Category definition

Alert performance (AP) – **with** metabolic activation

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



CAS 56-18-8

**Alert performance results...**

Alert Category	Positive (%)	Negative (%)	Count
Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	81.25%	18.75%	16
Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS)	50.62%	49.38%	1458
Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes (Protein binding alerts for skin sensitization by OASIS)	55.89%	44.11%	399
Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	83.33%	16.67%	18

**Alert performance results...**

Alert Category	Strongly positive (%)	Weakly positive (%)	Negative (%)	Count
Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	71.43%	7.14%	21.43%	10
Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS)	27.30%	20.20%	52.50%	1381
Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes (Protein binding alerts for skin sensitization by OASIS)	31.23%	22.57%	46.19%	381
Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	75.00%	6.25%	18.75%	16

**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

The screenshot displays the QSAR TOOLBOX interface. A sidebar on the left shows 'Document 1 # CAS: 56188' and a tree view of alert categories including 'Suitable' and 'Plausible'. The main window shows 'Alert performance results...' for 'Protein binding alerts for skin sensitization by OASIS'. The table below summarizes the performance metrics for various alert criteria.

Alert Description	Positive (%)	Negative (%)	Chemicals
Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	81.25%	18.75%	16
Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS)	50.62%	49.38%	1458
Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes (Protein binding alerts for skin sensitization by OASIS)	55.89%	44.11%	399
Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	83.33%	16.67%	18

Annotations in red text and arrows point to the 'Show all(16)...' button for the first alert, labeled 'Calculated AP accounting for all defined criteria for the parent and metabolites', and the 'Show all(399)...' button for the third alert, labeled 'Calculated AP for each of the alerts'.

# Category definition

Alert performance (AP) – **with** metabolic activation

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



CAS 56-18-8

The screenshot shows the QSAR TOOLBOX interface. The main window displays 'Alert performance results...' for the chemical CAS: 56188. The results are summarized in the following table:

Alert Description	Positive (%)	Negative (%)	Total Count
Using of "Skin metabolism simulator" (Combined parent and products requirements: No alert found <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes <AND> Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS))	81.25%	18.75%	16
Using of "Skin metabolism simulator" (Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS))	50.62%	49.38%	1458
Using of "Skin metabolism simulator" (Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes (Protein binding alerts for skin sensitization by OASIS))	55.89%	44.11%	399
Using of "Skin metabolism simulator" (Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS))	83.33%	16.67%	18

The alert with 83.33% positive performance is highlighted with a red box, and a red arrow points to it with the text: **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](#)