

OECD QSAR Toolbox v.3.1

Example for predicting skin sensitisation potential of (2*E*,6*Z*)-2,6-nonadien-1-ol accounting for skin metabolism

Outlook

- **Background**
- Objectives
- The exercise
- Workflow

Background

- This is a step-by-step presentation designed to take the user through the Toolbox workflow for filling data gap for skin sensitization of trans-2,cis-6-nonadienol accounting for its skin metabolism

Outlook

- Background
- **Objectives**
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Objectives

This presentation demonstrates a number of functionalities of the Toolbox:

- Simulating skin metabolism of target chemical
- Identify analogues for a selected active metabolite
- Filling data gaps for active metabolites by read across
- Assign prediction of metabolite to the parent chemical

Outlook

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- Workflow

The Exercise

- In this exercise we will predict the skin sensitization potential for target chemical (**trans-2,cis-6-nonadienol**) [**CAS # 28069-72-9**].
- Profile the target chemical and identify no Protein binding alert for target chemical.
- Gather available experimental data for the target chemical and identify positive experimental data.
- Skin metabolism of target chemical will be accounted for.
- Read across prediction for active metabolite will be applied.
- The predicted result of metabolite will be assigned to the target chemical.

Outlook

- Background
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- **Workflow**

Workflow

- **As you know the Toolbox has 6 modules which are typically used in sequence:**
 - Chemical Input
 - Profiling
 - Endpoint
 - Category Definition
 - Data Gap Filling
 - Report
- **In this example we will use the modules in a different order, tailored to the aims of the example.**

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - **Input**

Chemical Input Overview

- This module provides the user with several means of entering the chemical of interest or 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.

Chemical Input

Ways of Entering a Chemicals

User Alternatives for input of Chemical:

A. Single target chemical

- Chemical Name
- Chemical Abstract Services (CAS) number (#)
- SMILES (simplified molecular information line entry system) notation/InChi
- Drawing chemical structure
- Select from User List/Inventory/Databases
- Chemical IDs such as EC number, ENECS number

B. Group of chemicals

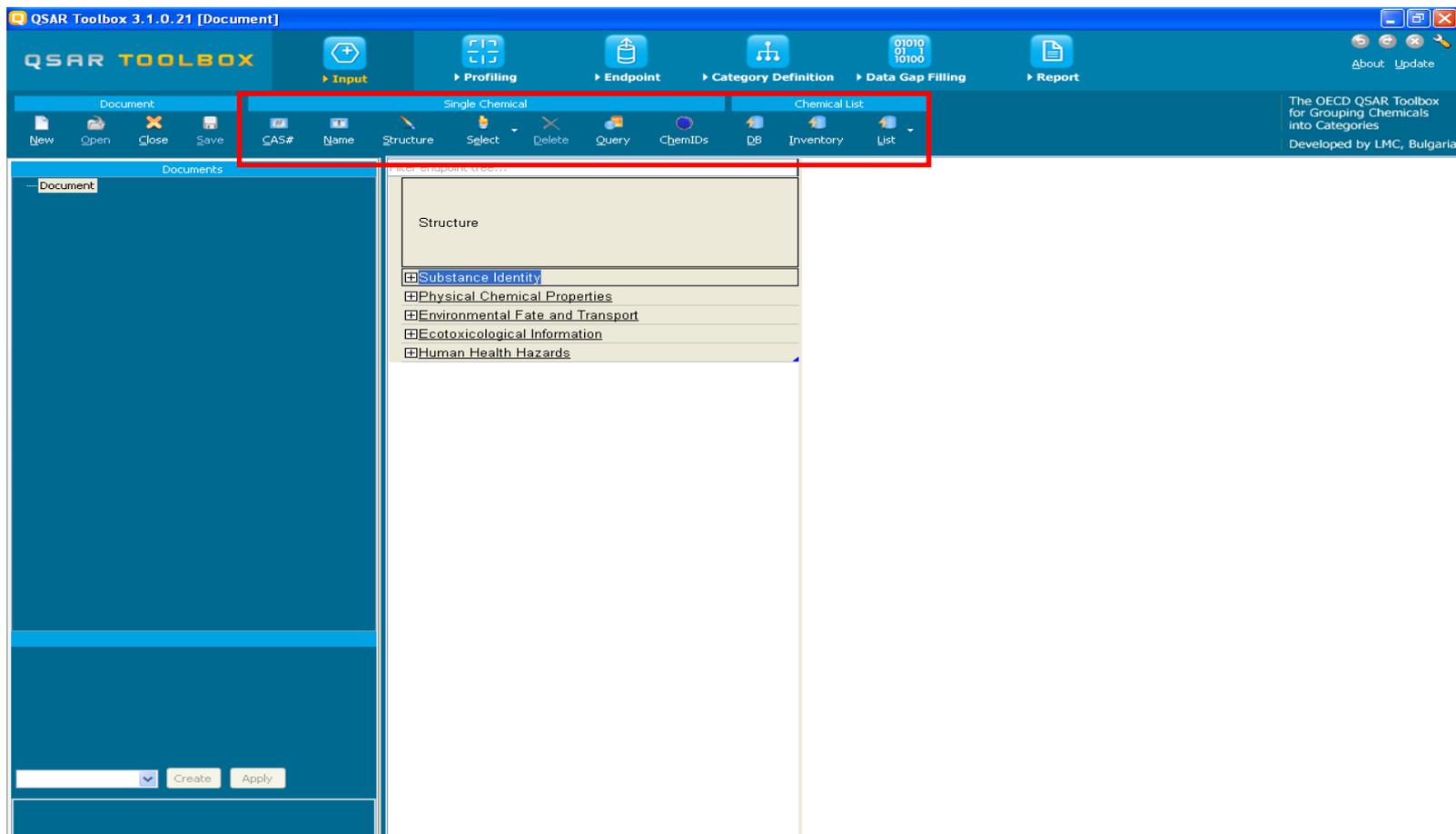
- User List/Inventory
- Specialized Databases

Chemical Input

Input Screen

- Open the Toolbox.
- The six modules in the workflow are seen listed next to “QSAR TOOLBOX” title.
- **Click** on “Input” (see next screen shot)

Chemical Input Input Screen



Chemical Input

Input target chemical by CAS#

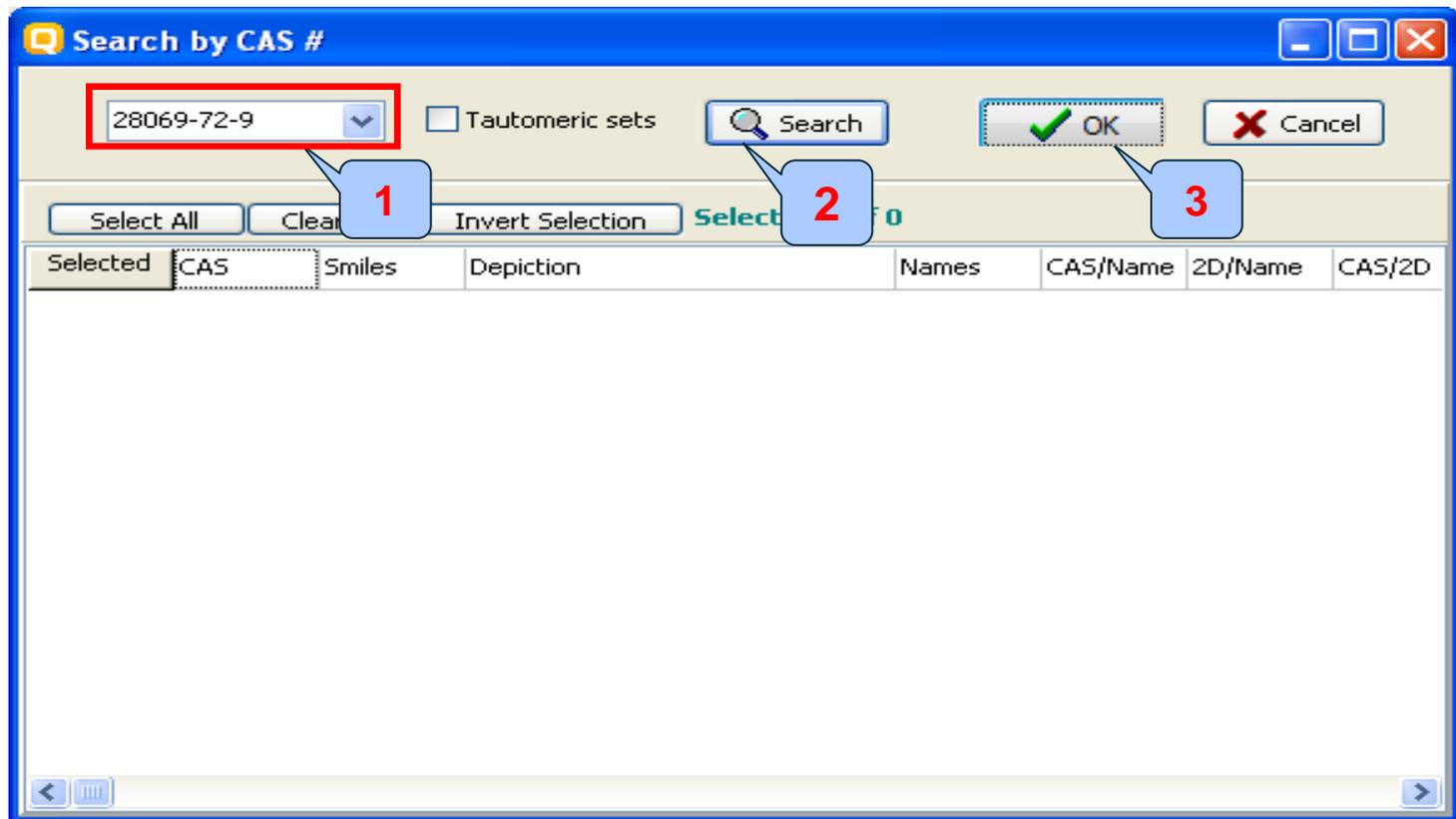
The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The 'Input' menu is active, and the 'CAS#' button is highlighted with a red box and a callout bubble containing the number '1'. The main window displays a 'Filter endpoint tree...' panel with the following options:

- Structure
- Substance Identity
- Physical Chemical Properties
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards

A blue box at the bottom of the screenshot contains the text: **1. Click on CAS#**

Chemical Input

Enter CAS# of trans-2,cis-6-nonadienol



1. **Enter** the CAS# In the blank field; 2. **Click** Search button; 3. **Press** OK

Chemical 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-dimensional depiction.

Selected	CAS	Smiles	Depiction	Names	CAS/Name	2D/Name	CAS/2D
1. Yes	28069-72	C(=CCCC		1: trans-2 2: (2e,6z) 3: 2,6-nor 4: 2,6-nor	1: Low Qu 1: Skin 2: High Qu 1: ECL 2: EIN 3: REA 3: High Qu 1: AIC 2: Car 4: Low Qu 1: TSO	1: Low Qu 2: High Qu 3: High Qu 1: Car 4: N/A	1: High

1. **Click** OK to enter the target structure into data matrix

Chemical Input

Target chemical identity

- **Double click** "Substance Identity" displays the chemical identification information.
- The user should note that existing names of the target chemical are presented in different colours. This indicates the reliability of relation CAS-Name for the target chemical(see next screen shots).
- The workflow on the first module is now complete, and the user can proceed to the next module.

Chemical Input

Target chemical identity

The screenshot displays the QSAR Toolbox 3.1.0.21 interface. The main window is titled "QSAR Toolbox 3.1.0.21 [Document]". The top menu bar includes "Input", "Profiling", "Endpoint", "Category Definition", "Data Gap Filling", and "Report". Below the menu bar, there are tabs for "Document", "Single Chemical", and "Chemical List". The "Single Chemical" tab is active, showing a "Filter endpoint tree..." panel on the left and a "1 [target]" panel on the right. The "Filter endpoint tree..." panel lists various categories such as "Substance Identity", "Physical Chemical Properties", "Environmental Fate and Transport", "Ecotoxicological Information", and "Human Health Hazards". The "1 [target]" panel displays the chemical structure and its identity information, including the CAS Number (28069-72-9), EINECS Number (248...), and Chemical Name (trans-2,cis-6-nonadien-2,6-diol, (2E,6Z)-nona-2,6-dien-1-ol, (...)). The chemical name is highlighted with a red circle. The bottom of the interface shows a "Create" and "Apply" button.

Chemical Input

Target chemical identity

The colour code indicates the reliability of the chemical identifier:

- **Green:** There is a high reliability between the identifier and the structure. This colour is applied if the identifier is the same in several quality assured databases.
- **Yellow:** There is only a moderate reliability between the identifier and the structure. The colour is applied if the identifier is the same in several databases for which the quality assurance could not be established.
- **Red:** There is a poor reliability between the identifier and the structure. The colour is applied if the identifier is allocated to different structures in different databases.

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - **Profiling**

Profiling Overview

- “Profiling” refers to the electronic process of retrieving relevant information on the target compound, other than environmental fate, ecotoxicity and toxicity data, which are stored in the Toolbox database.
- Available information includes likely mechanism(s) of action, as well as observed or simulated metabolites.

Profiling

Side-Bar to Profiling

- For most of the profilers, background information can be retrieved by highlighting one of the profilers (for example, Protein binding by OASIS v1.1 and clicking on “View” (see next screen shot)).

Profiling Side-Bar to Profiling

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The top menu bar includes 'Input', 'Profiling', 'Endpoint', 'Category Definition', 'Data Gap Filling', and 'Report'. The 'Profiling' menu is open, showing options like 'Apply', 'New', 'View', and 'Delete'. The 'View' option is circled in red and labeled '2'. The 'Profiling methods' sidebar on the left lists various methods, with 'Protein binding by OASIS v1.1' circled in red and labeled '1'. The 'Advanced' Profiling Scheme Browser window is open, showing a tree view of categories. The 'Aldehydes' category is highlighted in red and labeled '3'. The 'Textual description' pane on the right provides a detailed description of the mechanism for Schiff base formation with aldehydes, including a chemical reaction scheme and references.

1. **Highlight** the profiler
2. **Click** View
3. **Click** Advance in order to see detailed description of highlighted category (in this case "Aldehydes")

Profiling Side-Bar to Profiling

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The top menu bar includes 'Input', 'Profiling', 'Endpoint', 'Category Definition', 'Data Gap Filling', and 'Report'. The 'Profiling' menu is open, showing 'View' circled in red with a '2' callout. In the 'Profiling methods' sidebar, 'Protein binding by OASIS v1.1' is circled in red with a '1' callout. The 'Protein binding by OASIS v1.1 - Profiling Scheme Browser' window shows a tree view of category definitions, with 'Aldehydes' circled in red. The 'Structural boundaries' window shows a logical expression with 'AND' and 'OR' operators circled in red. Below, the 'Boundary Options' panel shows the 'Metabolism' tab with the fragment CC(=O)O and a chemical structure diagram of an aldehyde labeled 'Structural fragment'.

1. **Highlight** the profiler
2. **Click** View
3. **Select** "Aldehydes"

Profiling

Profiling the target chemical

- The outcome of the profiling determines the most appropriate way to search for analogues (detailed information about profilers could be found in “Manual for Getting started” (Chapter 4) published on the OECD website:
<http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm>
- Table 4 - 1 in chapter 4 (Manual for getting started) lists a selection of profilers and their relevance for different endpoints of regulatory relevance
- The following profiling schemes are relevant to the **Skin sensitization**:
 - Protein binding by OASIS v.1.1 – general mechanistic
 - Protein binding by OECD – general mechanistic
 - Protein Binding Potency – general mechanistic
 - Protein binding alerts for skin sensitization by OASIS v1.1 – endpoint specific

Profiling

Profiling the target chemical

- This selects (a **green** check mark appears) or deselects (**green** check mark disappears) profilers.
- For this example, go through the general and endpoint specific profiling mechanisms and highlight those that apply to skin sensitization(see next screen shot).

Profiling

Profiling the target chemical

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The 'Profiling' tab is active. In the 'Profiling methods' panel, the following checkboxes are selected:

- Ionization at pH = 9
- Protein binding by OASIS v1.1
- Protein binding by OECD
- Protein binding potency
- Skin sensitization alerts for skin sensitization by OASIS v1.1
- ICHER Expert System ver. 1 - USEPA

The 'Apply' button in the top-left corner of the Profiling methods panel is circled in red. A callout labeled '2' points to it. Another callout labeled '1' points to the 'Protein binding by OASIS v1.1' checkbox. A third callout labeled '1' points to the 'Skin sensitization alerts for skin sensitization by OASIS v1.1' checkbox. The 'Metabolism/Transformations' panel is also visible at the bottom.

The main window displays the chemical structure of the target and a list of endpoints to be profiled, including Substance Identity, Physical Chemical Properties, Environmental Fate and Transport, Ecotoxicological Information, and Human Health Hazards.

1. Check protein binding profiles from **General Mechanistic** and **Endpoint specific** group: **Protein binding for skin sensitization by OASIS** profiler
2. Click Apply

Profiling

Profiling the target chemical

- The actual profiling will take up to several seconds depending on the number and type of profilers selected
- The results of profiling automatically appear as a dropdown box under the target chemical (see next screen shot)
- Please note the specific protein-binding profilers
- No protein binding alert has been found for the test compound (trans-2,cis-6-nonadienol).

Profiling

Profiling the target chemical

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The main window displays the Profiling module with a tree view of endpoints. The 'Profile' node is selected and expanded, showing the following results:

Endpoint	Result
Protein binding by OASIS v1.1	No alert found
Protein binding by OECD	No alert found
Protein binding potency	Not possible to classify according to...
Endpoint Specific	
Protein binding alerts for skin sensitization by OASIS v1.1	No alert found

The chemical structure of the target is shown as a long-chain alkane with a terminal functional group.

1. Double click on "Profile" node to review the profiling results.

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - **Endpoint**

Endpoint Overview

- “Endpoint” refers to the electronic process of retrieving the environmental fate, ecotoxicity and toxicity data that are stored in the Toolbox.
- Data gathering can be executed in a global fashion (i.e., collecting all data for all endpoints) or on a more narrowly defined basis (e.g., collecting data for a single or limited number of endpoints).

Endpoint

Case study

- In this example, we limit our data gathering to a single toxicity endpoint (skin sensitization).
- In this example, we collect data from the databases containing experimental results for Skin sensitisation (Skin sensitisation and Skin sensitisation ECETOC).
- **Click** on “Endpoint” in the Toolbox workflow.
- **Expand the** “Human Health Hazards” section
- **Click** on the box to select the relevant databases.
- **Click** on “Gather data” (see next screen shot).

Endpoint Gather data

1

2

3

4

1. **Click** Endpoint
 2. **Expand** the Human Health Hazards section
 3. **Select** databases related to the target endpoint
 4. **Click** Gather

Endpoint

Gather data

- Toxicity information on the target chemical is electronically collected from the selected dataset(s)
- It should be kept in mind that the search for data and analogues is performed only among the chemicals which are listed in the selected databases, which in this example are **Skin sensitization** and **Skin sensitization ECETOC**
- In this example, there is Positive experimental data for the target chemical(see next screen shots)

Endpoint Gather data

Toxicity information on the target chemical is electronically collected from the selected datasets. A window with "Read data?" appears. Now the user could choose to collect "all" or "endpoint specific" data.

The screenshot displays the QSAR Toolbox 3.1.0.21 interface. The main window shows the 'Endpoint' workflow selected in the top menu. On the left, a 'Databases' list includes 'Human Health Hazards' with several sub-items checked, such as 'Skin sensitization' and 'Skin sensitization ECETOC'. The central area shows a 'Filter endpoint tree...' with a 'Structure' field containing a chemical structure and a list of categories like 'Substance Identity', 'Physical Chemical Properties', etc. A 'Read data?' dialog box is overlaid on the screen, featuring a red callout bubble with the number '1' pointing to the 'OK' button. The dialog box contains the following options: 'All endpoints' (selected), 'Choose...', 'from Tautomers' (checked), and 'OK' and 'Cancel' buttons.

1. Click OK to read all available data

Endpoint Gather data

The screenshot displays the QSAR Toolbox 3.1.0.21 interface during the 'Endpoint' workflow. The 'Databases' panel on the left shows 'Human Health Hazards' selected. The 'Filter endpoint tree...' panel in the center shows a tree view with 'Skin' expanded to 'In Vivo', which is further expanded to 'GPMT' and 'LLNA'. A callout box with the number '1' points to the 'GPMT' node. The 'Datamatrix' panel on the right shows a table with one row containing '(1/1) M: Positive' and a chemical structure.

1. Available experimental data appears on datamatrix.

Endpoint Gather data

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The 'Endpoint' tab is active, displaying a filter endpoint tree on the left and a chemical structure in the center. A 'Data points' window is open, showing a table of data points. The table has columns for #, Endpoint, Value, Original value, Organ, Reference source, Institution and country, Year, Type of method, Title, Data from tautomer structure, QA (CAS-2D), Database name, Assigned SMILES, Comment, Author, and Assay. The first row contains the following data:

#	Endpoint	Value	Original value	Organ	Reference source	Institution and country	Year	Type of method	Title	Data from tautomer structure	QA (CAS-2D)	Database name	Assigned SMILES	Comment	Author	Assay
1	S M W N	Positive	Strong sensitizer	Skin	SAR QSAR Environ. Res. 2(3): 159-179	LMC,BUL	1994	In Vivo	Multivariate QSAR analysis of a skin sensitization database.	No	N/A	Skin sensitization	YES	Strong sensitizer = Animals showing positive response > 30%; Weak sensitizer	Cronin M. T., Basketter D. A.	GPMT

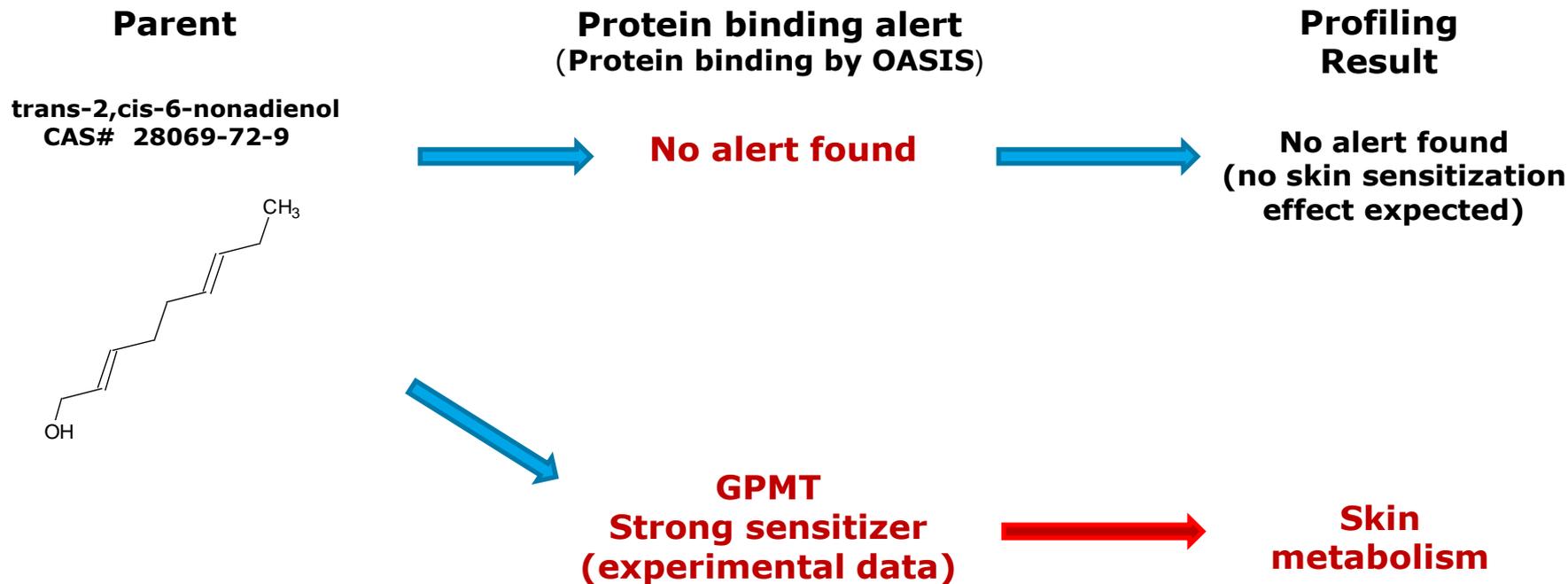
Callout 1 points to the cell containing '(1/1) M: Positive'. Callout 2 points to the 'X' button in the top right corner of the 'Data points' window.

1. **Double-click** on the cell displays metadata information for the observed data
2. **Click** on the X to close the window

Recap

- The first module, which introduces the target chemical, ensure correctness of the structure
- The second module shows that there is no protein binding alert for target chemical
- In the third module, you have found that the target chemical has positive skin sensitization data
- The positive experimental data could be due to skin metabolism
- The study continues with accounting for skin metabolism of target chemical(see next slides).

Recap



Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - **Handling of skin metabolism**

Handling of skin metabolism of target chemical

- Multiplying target chemical by skin metabolism simulator
- Multiplying target chemical by skin metabolism simulator is accomplished in section **Input**
- The generated metabolites appear in tree like form(see next screen shot)

Handling of skin metabolism of target chemical

Multiplication of target chemical

1. **Click** on the SMILES of the target chemical and perform right click on it, then
2. **Select** Multiplication-Metabolism/Transformations
3. **Select** Skin metabolism simulator
4. Generated metabolites appear in tree like form

Handling of skin metabolism of target chemical

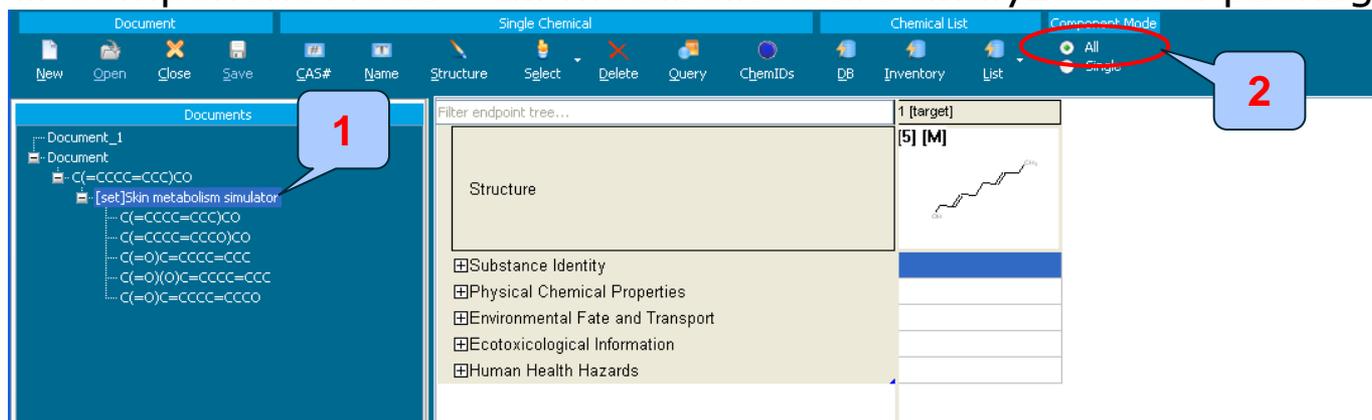
Visualization of modeling modes

- Two component modes are implemented:
 - **Set Mode** - all metabolites are analyzed as a package
 - **Individual Component Mode** - each metabolite is analyzed individually(see next screen shot)

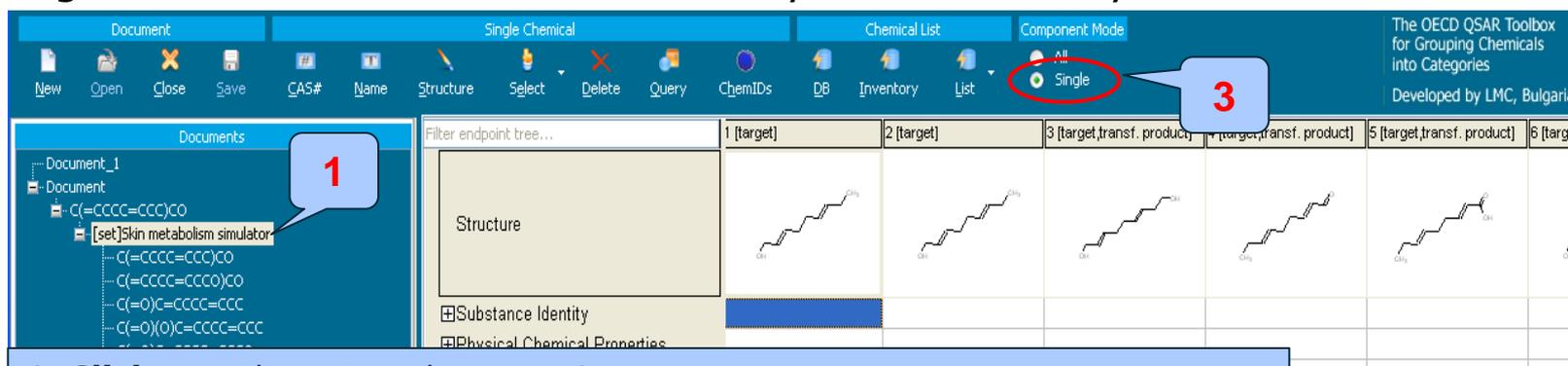
Handling of skin metabolism of target chemical

Visualization of modeling modes

- All Component Mode – all metabolites are analyzed as a package



- Single Mode – each metabolite is analyzed individually



1. **Click** over the set as shown on 1
2. **All** component mode – select All (2)
3. **Single** component mode – select Single (3)

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - **Handling of skin metabolism of target chemical**
 - **Profiling set of metabolites**

Handling of skin metabolism of target chemical

Profiling set of metabolites

- This module identifies profilers of target chemical and its metabolites
- Protein binding profiles related to skin sensitization are applied on package of target and metabolites
- Profiling results of target and metabolites are illustrated in Single Component mode
- Click on "**Profiling**" to go to the required module
- Apply **Protein binding profilers**(see next screen shot)

Handling of skin metabolism of target chemical

Protein binding result of parent and metabolites

3

1

2

2

The profiling results indicates no protein binding alerts or target chemical. However, two of simulated metabolites exhibit interaction with proteins via two different protein binding mechanisms.

	1 [target]	2 [target]	3 [target,transf. product]	4 [target,transf. product]	5 [target,transf. product]	6 [target,transf. product]
Structure						
Physical Chemical Properties						
Environmental Fate and Transport						
Ecotoxicological Information						
Human Health Hazards						
Profile						
General Mechanistic						
Protein binding by OASIS v1.1	No alert found	No alert found	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio...	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio...
Protein binding by OECD	No alert found	No alert found	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff Base Formers Schiff Base Former...	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff Base Formers Schiff Base Former...
Protein binding potency	Not possible to classify...	Not possible to cla...	Not possible to cla...	Highly reactive (GSH) Highly reactive (GS...	Not possible to cla...	Highly reactive (GSH) Highly reactive (GS...
Endpoint Specific	No alert found	No alert found	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio...	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio...
Protein binding alerts for skin sensitization by OAS...						

1. Go to Profiling 2. Check the profilers related to the target endpoints 3. Click Apply

Handling of skin metabolism of target chemical

Recap

- The profiling results indicates no protein binding for target chemical
- Two of simulated skin metabolites have positive protein binding alerts
- One of the reactive metabolites is used for further read across analysis
- The next two parts of the exercise will focus one of the reactive metabolites and find similar analogues of the reactive one (see next screenshot).

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - **Handling of skin metabolism of target chemical**
 - Profiling set of metabolites
 - **Focus of active metabolite**

Handling of skin metabolism of target chemical

Focus of active metabolite

This metabolite is selected for further read-across prediction

1

2

“Focus” functionality allows the selected metabolite to be used as post target representative of the target chemical

1. **Right click** over the active metabolite
2. **Select** Focus from the appeared menu

1 [target]	2 [target]	3 [target,transf. product]	4 [target,transf. product]	5 [target,transf. product]	6 [target,transf. product]
No alert found	No alert found	No alert found	Michael addition Michael addition >>...		
No alert found	No alert found				
Not possible to cla...	Not possible to cla...	Not possible to cla...	Schiff base formation Highly reactive (GSH) Highly reactive (GS...	Not possible to cla...	Schiff base formation Highly reactive (GSH) Highly reactive (GS...
Alert found	No alert found		Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio... Schiff base formatio...	No alert found	Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio... Schiff base formatio...

Handling of skin metabolism of target chemical Focus of active metabolite

The screenshot displays the QSAR Toolbox 3.1.0.21 interface. On the left, a tree view under 'Documents' shows a hierarchy: 'C(=CCCC=CCC)CO' -> '[set]Skin metabolism simulator' -> 'C(=CCCC=CCC)CO' -> 'C(=O)C=CCCC=CCC' (highlighted with a red circle). Below the tree, the chemical structure of 'C(=O)C=CCCC=CCC' is shown. The main window displays the 'Structure' tab with the chemical structure of the metabolite circled in red. A data matrix on the right lists various endpoints for this metabolite, including 'Michael addition', 'Schiff base formation', and 'Highly reactive (GSH)'. A blue box at the bottom contains the text: 'The selected metabolite appears in a new data matrix.'

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - **Handling of skin metabolism of target chemical**
 - Profiling set of metabolites
 - Focus of active metabolite
 - **Defining category for active metabolite**

Category Definition

Grouping methods

- The different grouping methods allow the user to group chemicals into chemical categories according to different measures of “similarity” so that within a category data gaps can be filled by read-across.
- Detailed information about grouping chemical (Chapter 4) could be found in document “Manual for Getting started” published on OECD website:

<http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm>

Basic guidance for category formation and assessment

Suitable categorization phases:

1. Structure-related profilers
2. Endpoint specific profilers (for sub-cat)
3. Additional structure-related profilers, if needed to eliminate dissimilar chemicals (to increase the consistency of category) (e.g. chemical elements)

Performing categorization:

1. The categorization phases should be applied successively
2. The application order of the phases depend on the specificity of the data gap filling
3. More categories of same Phase could be used in forming categories
4. Some of the phases could be skipped if consistency of category members is reached

Graphical illustration of suitable categorization phases is shown on next slide

Suitable Categorization/Assessment Phases

Phase I. Structure based

- US EPA Categorization
- OECD Categorization
- Organic functional group
- Structural similarity
- ECOSAR

**Broad grouping
Endpoint Non-specific**

Repeating Phase I due to Multifunctionality of chemicals

Phase II. Mechanism based

- DNA binding mechanism
- Protein binding mechanism
- Genotoxicity/carcinogenicity
- Cramer rules
- Verhaar rule
- Skin/eye irritation corrosion rules

**Subcategorization
Endpoint Specific**

Metabolism accounted for

Phase III. Eliminating dissimilar chemicals

**Apply Phase I – for structural dissimilarity
Filter by test conditions – for Biological dissimilarity**

**Subcategorization
Endpoint Specific**

Handling of skin metabolism of target chemical

Category definition for active metabolite

- In this exercise, the reactive metabolite is classified as: Aldehyde by US-EPA New chemical category (phase I)
- The identified Protein binding profiler of the reactive metabolite is: Michael addition >> a,b-unsaturated carbonyl compounds >> Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes (phase II)
- In order to expand the initial group of identified analogues the US-EPA New chemical category is used for categorization purposes (phase I).
- Searching for similar analogues is accomplished using the two skin sensitization databases: Skin sensitization and Skin sensitization ECETOC

Handling of skin metabolism of target chemical

Defining US-EPA category

- The category **US-EPA New chemical category (strict)** is used
- **Strict** functionality means that the software will identify analogues having **ONLY** the categories of the target (i.e aldehydes) and will exclude the analogues having any other categories
- **Select** US-EPA New Chemical category
- **Click** Define (see next screen shots)

Handling of skin metabolism of target chemical

Defining US-EPA category

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The 'Category Definition' tab is active. In the 'Grouping methods' list on the left, 'US-EPA New Chemical Categories' is highlighted with a red circle and labeled '1'. The 'Define' button in the top toolbar is circled in red and labeled '2'. A dialog box titled 'US-EPA New Chemical Categories' is open, showing 'Aldehydes (Acute toxicity)' selected in the 'Target(s) profiles' list, labeled '4'. The 'Strict' checkbox is checked in the dialog, labeled '3'. The 'OK' button is also visible.

1. **Highlight** "US-EPA New Chemical Categories" 2. **Click** Define 3. **Select** Strict 4. **Click** OK to confirm the category **Aldehydes (Acute toxicity)** defined by US-EPA category.

Handling of skin metabolism of target chemical

Defining US-EPA category

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The 'Category Definition' tab is active. A 'Define category name' dialog box is open, showing the category name 'Strict (US-EPA New Chemical Categories)' for 56 chemicals. A red callout box with the number '1' points to the 'OK' button. A blue instruction box at the bottom reads '1. Click OK to confirm the name of the category'.

Handling of skin metabolism of target chemical

Category analogues

- The Toolbox now identifies all chemicals corresponding to *Aldehydes(Acute toxicity)* by US-EPA listed in the skin sensitization databases.
- 56 analogues including the target chemical are identified; they form a mechanistic category named “**Aldehydes (Acute toxicity)**”, which will be used for further data gap filling.
- The experimental data for analogues in the category appears on datamatrix

Handling of skin metabolism of target chemical

Summary information for Analogues

The experimental results for the analogues appeared on datamatrix

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The main window displays a datamatrix table with columns for chemical structures and data points. A red box highlights a cell in the 'Human Health Hazards' section, specifically under 'Acute Toxicity', containing the text 'AOP (55/92)' and 'M: Negative'. A callout bubble with the number '1' points to this cell. The table also shows chemical structures for various compounds, including a long-chain alkane, a benzene ring with a substituent, a branched alkane, a benzene ring with a substituent, a chlorinated benzene ring, and formaldehyde (H₂C=O).

Structure	1 [target.transf. product]	2	3	4	5	6	7	8
Structure	<chem>CCCCCCCCCCCC</chem>	<chem>c1ccc(cc1)C(=O)O</chem>	<chem>CCCCC=O</chem>	<chem>c1ccc(cc1)C=O</chem>	<chem>ClC1=CC=C(Cl)C=C1</chem>	<chem>H2C=O</chem>	<chem>CCCCCCCCCCCC</chem>	
Human Health Hazards								
Acute Toxicity	AOP (55/92)	M: Negative	M: Negative	M: Negative, Negati...	M: Negative, Positiv...	M: Positive, Positiv...	M: Negative	M: P

Chemical statistic (1) presenting number of chemicals and the available experimental data

Recap

- In this case "US-EPA New-category Aldehydes(strict) is used for categorization purposes.
- The defined category consist of 56 analogues along with the target chemical
- The available experimental data for these 56 analogues have been collected from two skin sensitization databases.
- But before the user can proceed with the "Filling Data Gap" module, he/she should navigate through the endpoint tree and find the specific gap that will be filled in (in this case Human Health Hazards#Sensitisation#Skin#In Vivo).
- In this case we mixed assays and endpoints (see slides #62-64)

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - **Handling of skin metabolism of target chemical**
 - Profiling set of metabolites
 - Focus of active metabolite
 - Category definition for active metabolite
 - **Data gap filling**

Data gap filling

Apply Read across

The screenshot shows the QSAR Toolbox interface with the 'Data Gap Filling' workflow selected. The left sidebar contains options for 'Read-across', 'Trend analysis', and '(Q)SAR models'. The main window displays a table of chemical structures and their predicted values for various endpoints. A red circle highlights a cell in the 'Sensitisation/Skin/In vivo' row for a chemical, with a callout '1' pointing to it. Another red circle highlights the 'Read-across' option in the sidebar, with a callout '2' pointing to it. A third red circle highlights the 'Apply' button at the top left, with a callout '3' pointing to it.

Structure	1 [target.transf. product]	2	3	4	5	6
Structure	<chem>CCCCCCCC</chem>	<chem>CCCCCCCC</chem>	<chem>CCCCCCCC</chem>	<chem>CCCCCCCC</chem>	<chem>CCCCCCCC</chem>	<chem>H2C=O</chem>
Physical Chemical Properties						
Environmental Fate and Transport						
Ecotoxicological Information						
Human Health Hazards						
Acute Toxicity						
Carcinogenicity						
Developmental Toxicity / Terato...						
Genetic Toxicity						
Immunotoxicity						
Irritation / Corrosion						
Neurotoxicity						
Repeated Dose Toxicity						
Sensitisation						
Skin						
In Chemo						
In Vitro						
In Vivo	(55/86)	M: Negative	M: Negative	M: Negative, Negati...	M: Negative, Positiv...	M: Positive, Posi
Toxicity to Reproduction						
Toxicokinetics, Metabolism and ...						
Profile						
General Mechanistic						
Protein binding by OASIS v1.1						

1. Click on the cell corresponding to "Sensitisation/Skin/In vivo" for the target chemical(active metabolite) **2. Select** Read-across **3. Click** Apply

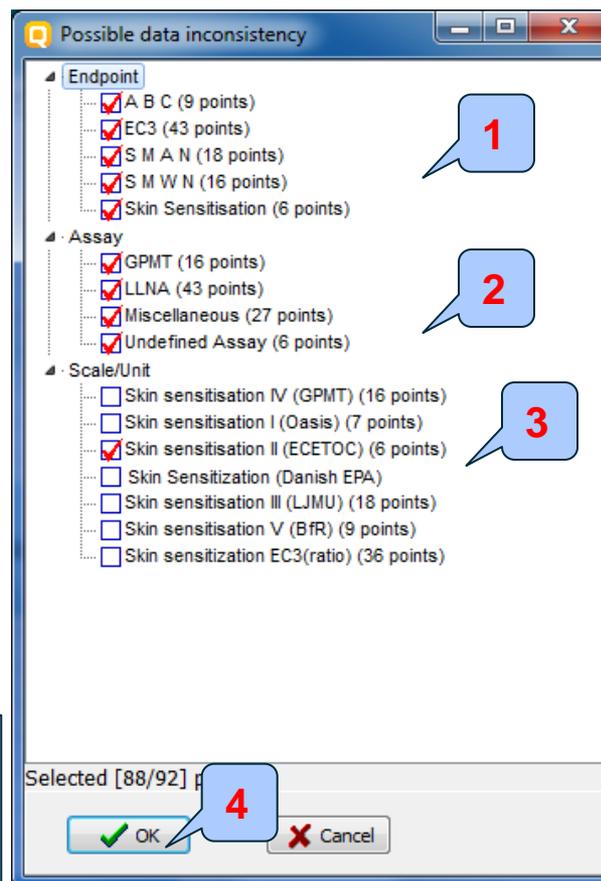
Data gap filling for active metabolite

Scale definition

- Skin sensitisation is “qualitative” endpoint for which the results are presented with categorical data (for example: positive; negative; weak sensitizer; strong sensitizer ,etc).
- Skin sensitisation potential of the chemicals came from different authors coded with different names (for example: data from John Moores University of Liverpool are: *Strongly sensitizing, Moderately sensitizing etc.*; data from European centre for Ecotoxicology and Toxicology of chemicals are: *Positive, Negative, and Equivocal*).
- The main purpose of the scales is to unify all data available in the Toolbox databases for a certain endpoint.
- The default scale for Skin Sensitisation is “Skin Sensitisation ECETOC”. It converts all skin data into: Positive, Negative, and Equivocal.

Data gap filling for active metabolite

Scale definition



1. In this case all endpoints (1) and assays (2) related to skin sensitization are taken into account
2. Default scale is Skin sensitization II (ECETOC)
3. Click OK to enter data gap filling

Data gap filling for active metabolite

Read-across

- The resulting plot is experimental results of all analogues (Y axis) according to a descriptor (X axis) with the default descriptor of log Kow (see next screen shot).
- The **RED** dot represents predicted results for the target chemical .
- The **BROWN** dots represent the experimental results available for the analogues that are used for the read-across.
- The **BLUE** dot represent the experimental results available for the analogues but not used for read-across.

Data gap filling for active metabolite Read-across

QSAR Toolbox 3.1.0.21 [Document_1]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition **Data Gap Filling** Report

About Update

The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Filling

Apply

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

Target Endpoint

Human Health Hazards Sensitisation Skin In Vivo

Structure	1 [target.transf. product]	2	3	4	5	6
	(55/66)	M. Negative	M. Negative	M. Negative, Negati...	M. Negative, Positiv...	M. Positive, Pos

Descriptors Prediction

Read across prediction of A B C, EC3, 5 M A N, 5 M W N, taking the highest mode from the nearest 5 neighbours, based on 5 values from 5 neighbour chemicals, Observed target value: N/A, Predicted target value: 'Positive'

Positive

Negative

log Kow

Descriptor X: log Kow

Accept prediction

Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Visual options
- Information
- Miscellaneous

56 Aldehydes (Acute toxicity) Strict (US-EPA New Chemical Categories) 3 Data gap filling 0/100 2/10

Data gap filling for active metabolite Subcategorization

- After the available data has been retrieved, the user can then further subcategorize the results according to the following endpoint-specific subcategorizations (phase II, slide #55):
 - Protein binding by Oasis v1.1.
 - Protein binding by OECD
 - Protein binding potency
- These steps are summarized in the next screen shots.

Data gap filling for active metabolite

Subcategorization 1: Protein binding by OASIS v.1.1.

The screenshot displays the 'Subcategorization' window of the OECD QSAR Toolbox. The left sidebar shows a tree view of grouping methods, with 'Protein binding by OASIS v1.1' selected under the 'General Mechanistic' category. The main window shows a table of analogues with columns for target, trans, product, and predicted target. The 'Analogues' section is circled in red and labeled '3'. The right sidebar shows the 'Select/filter data' panel, with the 'Subcategorize' button circled in red and labeled '1'. The bottom of the main window shows a scatter plot of log Kow values for the selected chemicals.

1. Select filter data/subcategorize 2. Select Protein binding by OASIS v1.1. Note all analogues are in the same category (3) as the target chemical, so no further action is required.

Data gap filling for active metabolite

Subcategorization 2: Protein binding by OECD

The screenshot shows the 'Subcategorization' window in the QSAR Toolbox. The 'Target' field is set to 'Michael addition'. The 'Differ from target by' section has 'All categories' selected. The 'Metabolism/Transformations' section is expanded to 'Do not account metabolism Documented', where 'Protein binding by OECD' is highlighted. A table below shows chemical structures and their predicted values. A scatter plot shows log Row values. A 'Return to matrix' panel is visible on the right.

1 [target,transf. product]	2	3	4	5	6
<chem>CCCCCCCC</chem>	<chem>CCOC1=CC=C(C=C1)C</chem>	<chem>CC=CC=O</chem>	<chem>O=C1C=CC(=O)N1</chem>	<chem>ClC1=CC=C(C=C1)C(=O)O</chem>	<chem>H2C=O</chem>
	M. Negative	M. Negative	M. Negative, Negati...	M. Negative, Positiv...	M. Po...

Annotations in the image:

- 1**: Points to the 'Select/filter data' option in the 'Return to matrix' panel.
- 2**: Points to 'Protein binding by OECD' in the 'Do not account metabolism Documented' section.
- 3**: Points to the 'Direct Activation' option in the 'Differ from target by' section.
- 4**: Points to the 'Remove' button in the 'Selected 10 (45/55)' list.

- 1. Open** Select/filter data/Subcategorize
- 2. Select** Protein binding by OECD
- Green dots represent analogues having different Protein mechanism of interaction
- 4. Remove** dissimilar chemicals

Data gap filling for active metabolite

Subcategorization 3: Protein binding potency

The screenshot displays the 'Subcategorization' window of the QSAR Toolbox. On the left, a tree view shows various grouping methods, with 'Protein binding potency' selected and circled in red (callout 1). The main area shows a table of chemical structures and their predicted categories. A row of green dots in the plot area represents analogues belonging to different subcategories (callout 2). A 'Remove' button is visible at the bottom of the plot area (callout 3).

1 (target,transf. product)	3	5	6	7	8
<chem>CCCC=O</chem>	<chem>ClC(=O)C(=O)Cl</chem>	<chem>H2C=O</chem>	<chem>CCCCCCCC</chem>	<chem>C1=CC=C(C=C1)C=C</chem>	
(55/86)	M. Negative	M. Negative, Positiv.	M. Positive, Positiv.	M. Negative	M. Positive, Pos

1. **Select** Protein binding potency 2. Green dots represent analogues belonging to different subcategories 3. **Remove** dissimilar chemicals

Data gap filling for active metabolite

Results after subcategorization

QSAR Toolbox 3.1.0.21 [Document_1]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Filling
Apply

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

Target Endpoint

Human Health Hazards: Sensitisation Skin In Vivo

Structure	1 [target,transf. product]	15	17	26	28
In Vivo (56/67)	R: Positive	M: Positive	M: Positive	M: Positive	M: Positive
Toxicity to Reproduction					

Read across prediction of A B C, EC3, S M A N, S M W N, taking the highest mode from the nearest 5 neighbours, based on 4 years from neighbour chemicals, Observed target value: N/A, Predicted target value: 'Positive'

Positive

A B C, EC3, S M A N, S M W N (obs.)

Negative

log Kow

Descriptor X: log Kow

Accept prediction

Return to matrix

- Select/filter data
- Subcategorize
- Mark chemicals by descriptor value
- Filter points by test conditions
- Mark focused chemical
- Mark focused points
- Remove marked chemicals/points
- Clear existing marks
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Visual options
- Set units in figure title
- Set axes ranges
- Show intercorrelations
- Information
- Miscellaneous

Information

The current prediction was accepted

OK

1. The predicted result is **positive** 2. **Accept prediction** 3. **Click OK** 4. **Return to matrix**

Data gap filling for active metabolite

Read-across prediction

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The 'Data Gap Filling Method' is set to 'Read-across'. The 'Target Endpoint' is 'Human Health Hazards Sensitisation Skin In Vivo'. The main table displays a data matrix with 6 columns representing different chemical structures and 7 rows representing different prediction methods. A red circle highlights the prediction result for the 'Sensitisation' endpoint, which is '(56/87) R: Positive'.

Structure	1 [target,transf. product]	2	3	4	5	6
Structure	<chem>CCCCCCCC</chem>	<chem>O=Cc1ccc(O)cc1</chem>	<chem>CC=CC=O</chem>	<chem>O=Cc1ccccc1</chem>	<chem>O=C(Cl)C(Cl)=O</chem>	<chem>H2C=O</chem>
Immunotoxicity						
Irritation / Corrosion						
Neurotoxicity						
Repeated Dose Toxicity						
Sensitisation	(56/87) R: Positive	M: Negative	M: Negative	M: Negative, Negati...	M: Negative, Positiv...	M: Positive, Posi
Skin						
In Chemico						
In Vitro						
In Vivo						
Toxicity to Reproduction						
Toxicokinetics, Metabolism and...						
Profile						
General Mechanistic						
Protein binding by OASIS v1.1	Michael addition Michael addition >>... Michael addition >>... Schiff base formation Schiff base formatio... Schiff base formatio... Michael addition >>... Michael addition >>...	Schiff base formatio... Schiff base formatio...	Schiff base formatio... Schiff base formatio...	Schiff base formatio... Schiff base formatio...	Michael addition >>... Michael addition >>... Michael addition >>... Schiff base formatio... Schiff base formatio... Schiff base formatio... Schiff base formatio... Schiff base formatio...	Schiff base forme... Schiff base forme...
	Michael addition >>... Michael addition >>...	No alert found	Schiff Base Formers Schiff Base Former...	No alert found	Schiff Base Formers Schiff Base Former...	Schiff Base Form... Schiff Base Form...

The read-across prediction result for metabolite appears on data matrix

56 Aldehydes (Acute toxicity) Strict (US-EPA New Chemical Categories) 3 2/0/0

Data gap filling for active metabolite

Interpreting Read-across

- In this example, all analogues have same protein binding alerts
- All analogues exhibit positive skin sensitization
- The same positive sensitising potential is therefore predicted for the target (i.e. active metabolite).
- The prediction of metabolite is further transferred to the parent chemical using Independent MOA (see next screen shots)

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - **Handling of skin metabolism of target chemical**
 - Profiling set of metabolites
 - Focus of active metabolite
 - Category definition for active metabolite
 - Data gap filling
 - **Assigning prediction of active metabolite to parent**

Handling skin metabolism of target chemical

Assigning data to parent chemical

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. On the left, the 'Documents' tree shows a folder '[set] Skin metabolism simulator' circled in red with a '2' callout. Below it, a query filter is visible: [has pred][has 4 group(s)]C(=O). The center panel shows a 'Filter endpoint tree...' with a list of toxicity endpoints. The right panel is a data matrix table with columns for chemical structures (1-6) and rows for various endpoints. The row for '(56/87) R: Positive' is circled in red with a '1' callout. The table contains predictions for various endpoints like 'Acute Toxicity', 'Carcinogenicity', etc., with values like 'M: Negative' or 'M: Positive, Posi'.

1. The read-across prediction for the metabolite is positive then 2. **Select** datamatrix of the target chemical: click over the node "[set] Skin metabolism simulator"

Handling skin metabolism of target chemical

Assigning data to parent chemical

The screenshot displays the QSAR Toolbox 3.1.0.21 interface. On the left, a document tree shows a chemical structure with a skin metabolism simulator. The central panel shows the chemical structure and a hierarchical endpoint tree. The 'Skin' category is expanded, showing sub-categories: In Chemico, In Vitro, and In Vivo. The 'In Vivo' sub-category is selected, and the '(1/1)' cell is highlighted with a red circle and a blue callout '1'. The right panel shows a table of results for six target chemicals. The first three targets have 'No alert found', while the last three have alerts: 'Michael addition', 'Michael addition >>...', and 'Schiff base formation'. A blue callout '2' points to the 'Data Gap Filling' button in the top toolbar.

1. **Select** cell corresponding to skin sensitization 2. **Select** Data Gap Filling

Handling skin metabolism of target chemical

Assigning data to parent chemical

The screenshot displays the QSAR Toolbox interface with the following components:

- Top Bar:** Navigation tabs for Input, Profiling, Endpoint, Category Definition, Data Gap Filling, and Report.
- Left Panel:** 'Data Gap Filling Method' section with 'Independent MOA' selected (indicated by a red '1'). Below it, 'Target Endpoint' is set to 'Human Health Hazards Sensitisation Skin In Vivo'.
- Main Table:** A table with 6 columns representing different target endpoints. The first row shows chemical structures. Subsequent rows show a hierarchical tree of endpoints: Physical Chemical Properties, Environmental Fate and Transport, Ecotoxicological Information, Human Health Hazards (with sub-categories like Acute Toxicity, Carcinogenicity, etc.), Sensitisation (with sub-categories like Skin, In Chemico, In Vitro, In Vivo), Toxicity to Reproduction, Toxicokinetics, Metabolism and ..., Profile, and General Mechanistic. A red circle highlights the '(1/1)' value in the 'In Vivo' sub-category of 'Sensitisation' (indicated by a red '2').
- Bottom Row:** Alerts for 'Michael addition' are visible under columns 4 and 6.

- 1. Check Independent MOA**
- 2. Click Apply**

Handling skin metabolism of target chemical

Assigning data to parent chemical

- The following actions (steps) are used for assigning data to parent chemical:
 - Accept prediction
 - Return to matrix
- Final prediction for the parent compound labeled as CI (Component based Independent mode) is **positive** (see next screen shot)

Handling skin metabolism of target chemical

Assigning data to parent chemical

The screenshot displays the QSAR Toolbox 3.1.0.21 interface. The main window shows a comparison of a parent chemical (Column 1) and its metabolite (Column 2). The parent chemical is assigned the prediction '(2/2) Cl: Positive' (circled in red), and the metabolite is assigned 'R: Positive' (circled in red). A blue callout box with a white background and black text states: "The prediction for the metabolite is assigned to the parent chemical".

The interface includes a top menu bar with options: Input, Profiling, Endpoint, Category Definition, Data Gap Filling, and Report. The left sidebar shows the 'Filter endpoint tree...' with categories like Substance Identity, Physical Chemical Properties, Environmental Fate and Transport, Ecotoxicological Information, Human Health Hazards, and Profile. The main table displays chemical structures and various endpoint predictions for both the parent and metabolite.

Endpoint	1 [target]	2 [target]	3 [target,transf. product]	4 [target,transf. product]	5 [target,transf. product]	6 [target,transf. product]
Structure						
Substance Identity						
Physical Chemical Properties						
Environmental Fate and Transport						
Ecotoxicological Information						
Human Health Hazards						
Acute Toxicity						
Carcinogenicity						
Developmental Toxicity / Terato...						
Genetic Toxicity						
Immunotoxicity						
Irritation / Corrosion						
Neurotoxicity						
Repeated Dose Toxicity						
Sensitisation						
Skin		(2/2) Cl: Positive				
Toxicity to Reproduction						
Toxicokinetics, Metabolism and ...						
Profile						
General						
Protein						
Alerts	No alert found	No alert found	No alert found	Schiff base formatio... Michael addition	No alert found	Schiff base formo... Michael addition

Recap

- The target chemical **trans-2,cis-6-nonadienol** has been entered into the system.
- It has been profiled by Protein binding profilers; no protein binding has been found for target chemical.
- Positive experimental data has been retrieved for target chemical.
- Skin metabolism of target chemical is investigated. Two of simulated skin metabolites have positive protein binding alerts.
- These metabolites have similar protein binding alert: **α,β -unsaturated aldehydes**. One of the reactive metabolites is used for further read across analysis.
- No experimental data for the selected metabolite has been found, so the category of similar analogues has been defined.
- The initial group of analogues is defined by US-EPA New Chemical categories.
- 56 analogues including the target chemical are identified; they form a mechanistic category "**Aldehydes (Acute toxicity)**", which will be used for gap filling.
- Read-across is used for data gap filling.
- Protein binding categories have been used for refining the initial category.
- Positive skin sensitization has been predicted for the active metabolite.
- Positive prediction for reactive metabolite has been transferred to the parent chemical using Independent MOA.

Outlook

- Background
- Objectives
- The exercise
- **Workflow**
 - Input
 - Profiling
 - Endpoint
 - Handling of skin metabolism of target chemical
- **Report**

Report

- Remember the report module allows you to generate a report on the predictions performed with the Toolbox. This module contains predefined report templates as well as a template editor with which users can define their own user defined templates. The report can then be printed or saved in different formats.
- Generating the report is shown on next screenshots

Report

QSAR Toolbox 3.1.0.21 [Document_3]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Reports Repository

Create Print Close Save as Register Unregister Update Clone Design

Available data to report

- Predictions
- (Q)SARs
- Categories

Available report templates

- Standard (predefined)
 - QSAR Model Reporting Format (QMRF v.3.1)
 - QSAR Toolbox Category Report (CCRF v.3.1)
 - QSAR Toolbox Prediction Report (TPRF v.3.1)
- Custom (user defined)
 - Editable copy of QSAR Model Reporting Format (QMRF v.3.1)
 - Editable copy of QSAR Toolbox Category Report (CCRF v.3.1)
 - Editable copy of QSAR Toolbox Prediction Report (TPRF v.3.1)

show only relevant templates

Prediction [2]

Prediction of EC3 for nona-2,6-dien-1-ol 1 / 30

QSAR Toolbox prediction for single chemical using metabolism

(uses single component mode for handling of target chemical and its metabolites/transformation products)

The template of the current report is based on "GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIPS MODELS" published by OECD (September, 2007) and "GUIDANCE ON INFORMATION REQUIREMENTS AND CHEMICAL SAFETY ASSESSMENT / CHAPTER R.6: QSARS AND GROUPING OF CHEMICALS" published by ECHA (May, 2008).

The report provides information about the target substance, chemical characteristics used for the grouping, the resulting boundaries of the group of chemicals (applicability)

Report

The screenshot shows the QSAR Toolbox 3.1.0.21 interface. The main window displays a report titled "Prediction of EC3 for nona-2,6-dien-1-ol". The report content is as follows:

Prediction of EC3 for nona-2,6-dien-1-ol 4 / 30

QSAR Toolbox prediction for single chemical based on independent mode of action for metabolites/transformation products

Prediction of EC3 for nona-2,6-dien-1-ol

Summary

Toxicity of the target chemical (Positive) is predicted from its metabolites/transformation products using estimation based on 1 values (Positive x1) from 1 metabolites/transformation products having independent mode of action. Both experimental and predicted values for metabolites/transformation products are used in predicting the target toxicity.

Note that the information provided on the metabolites/transformation products is not linked to the possibility of their formation.

The target chemical FALLS within applicability domain of the prediction (see Section 4.3 for details).

The endpoint data is selected from the following database(s):

1. Skin sensitization
2. Skin sensitization ECETOC

Below is a summary table for endpoint & descriptor values for the target chemical and the metabolites/transformation products.
Experimental values from data matrix are presented in bold font. Recalculated endpoint values (if required by selected data usage option in Gap Filling) are presented in italic font. Recalculated endpoint values based on experimental data only are presented in bold and italic font.

1. Summary information for prediction

Report

Available data to report

- Predictions
- (Q)SARs
- Categories

Available report templates

- Standard (predefined)
 - QSAR Model Reporting Format (QMRF v.3.1)
 - QSAR Toolbox Category Report (CCRF v.3.1)
 - QSAR Toolbox Prediction Report (TPRF v.3.1)
- Custom (user defined)
 - Editable copy of QSAR Model Reporting Format (QMRF v.3.1)
 - Editable copy of QSAR Toolbox Category Report (CCRF v.3.1)
 - Editable copy of QSAR Toolbox Prediction Report (TPRF v.3.1)

show only relevant templates

Prediction [2]

1

h. Additional data eliminations (not determined by domain):
Not available

i. Predicted value (model result):
Positive

j. Predicted value (comments): *manually editable field*
Not provided by the user

4.3. Applicability domain (OECD Principle 3):
The target substance of current prediction is IN DOMAIN, because the target substances in all individual predictions are in domain
Below is the list of domain classification for the individual predictions (for details see the related prediction reports)
Individual component prediction No.1:
Target substance is IN DOMAIN

4.4. Uncertainty of the prediction (OECD Principle 4): *manually editable field*
Not provided by the user

4.5. Chemical and biological mechanisms (OECD Principle 5):
Profiling results for the target substance:
OECD HPV Chemical Categories
Not categorized
US-EPA New Chemical Categories

QSAR Toolbox 3.1.0.21
Database version: 3.4.4/3.1.2

QSAR TOOLBOX
TPRF v.3.1.1.31004

1. Predicted value

Report

Available data to report

- Predictions
- (Q)SARs
- Categories

Available report templates

- Standard (predefined)
 - QSAR Model Reporting Format (QMRF v.3.1)
 - QSAR Toolbox Category Report (CCRF v.3.1)
 - QSAR Toolbox Prediction Report (TPRF v.3.1)
- Custom (user defined)
 - Editable copy of QSAR Model Reporting Format (QMRF v.3.1)
 - Editable copy of QSAR Toolbox Category Report (CCRF v.3.1)
 - Editable copy of QSAR Toolbox Prediction Report (TPRF v.3.1)

Prediction [2]

h. Additional data eliminations (not determined by domain):
Not available

i. Predicted value (model result):
Positive

j. Predicted value (comments): *manually editable field*
Not provided by the user

4.3. Applicability domain (OECD Principle 3):
The target substance of current prediction is IN DOMAIN, because the target substances in all individual predictions are in domain
Below is the list of domain classification for the individual predictions (for details see the related prediction reports)

Individual component prediction No.1:
Target substance is IN DOMAIN

4.4. Uncertainty of the prediction (OECD Principle 4): *manually editable field*
Not provided by the user

4.5. Chemical and biological mechanisms (OECD Principle 5):

Profiling results for the target substance:

OECD HPV Chemical Categories
Not categorized

US-EPA New Chemical Categories

QSAR Toolbox 3.1.0.21
Database version: 3.4.4/3.1.2

QSAR TOOLBOX

TPRF v.3.1.1.31004

1. Applicability domain

The target chemical is "In domain", because the prediction of active metabolite is "In domain".

Report

The screenshot displays the QSAR Toolbox software interface. The main window shows a report for a single chemical component prediction. The report content is as follows:

Prediction of EC3 for nona-2,6-dien-1-ol 13

Appendix 7 - Chemical components

QSAR Toolbox prediction for single chemical based on independent mode of action for metabolites/transformation products

Prediction of EC3 for nona-2,6-dien-1-ol

APPENDIX 7 - Chemical components

Parent (target chemical):

- CAS number:**
7786-44-9
- Other regulatory numbers:**
Not reported
- Chemical name(s):**
nona-2,6-dien-1-ol
2,6-nonadien-1-ol

The interface includes a sidebar with 'Available data to report' (Predictions, QSARs, Categories) and 'Available report templates' (Standard and Custom). The top menu bar contains options like Input, Profiling, Endpoint, Category Definition, Data Gap Filling, and Report. A red oval highlights the main prediction title, and a blue callout bubble with the number '1' points to it.

1. Individual component prediction