

OECD QSAR Toolbox v.3.4

Predicting skin sensitisation potential of a chemical using skin sensitization data extracted from ECHA CHEM database

Outlook

- **Background**
- The exercise
- Workflow
- Save prediction

Background

- Read-across can be used to estimate missing data from a single or limited number of chemicals using an analogue approach. It is especially appropriate for “qualitative” endpoints for which a limited number of results are possible (e.g. positive, negative, equivocal).
- In the analogue approach, endpoint information for a single or small number of tested chemicals is used to predict the same endpoint for an untested chemical that is considered to be “similar”.
- Analogous sets of chemicals are often selected based on the hypothesis that the toxicological effects of each member of the category will show a common behaviour.
- In this test case ECHA Chem skin data are used in the read-across analysis

Side-Bar On Sensitization

- Allergic contact dermatitis that results from skin sensitization is a significant health concern.
- Skin sensitization is a toxicological endpoint that is complex and conceptually difficult.
- However, there is growing agreement that most organic chemicals must react covalently with skin proteins in order to behave as skin sensitizers.
- Therefore, mechanisms by which organic chemicals bind with proteins are relevant to grouping chemicals that may be skin sensitizing agents.

Outlook

- Background
- **The exercise**
- Workflow
- Save prediction

The Exercise

- In this exercise we will predict the skin sensitization potential for an untested compound, (bis(tert-butylidiodioxyisopropyl)benzene) [CAS # 25155-25-3], which will be the “target” chemical.
- This prediction will be accomplished by collecting a small set of test data for chemicals considered to be in the same category as the target molecule.
- The category will be defined by the structural alerts common to all the chemicals in the category.
- The additional data extracted from ECHA CHEM database will be used in order to expand the group of analogues
- The prediction itself will be made by “read-across”.
- The obtained prediction will be saved in a file

Outlook

- Background
- 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 Chemical

User Alternatives for Chemical ID:

A. Single target chemical

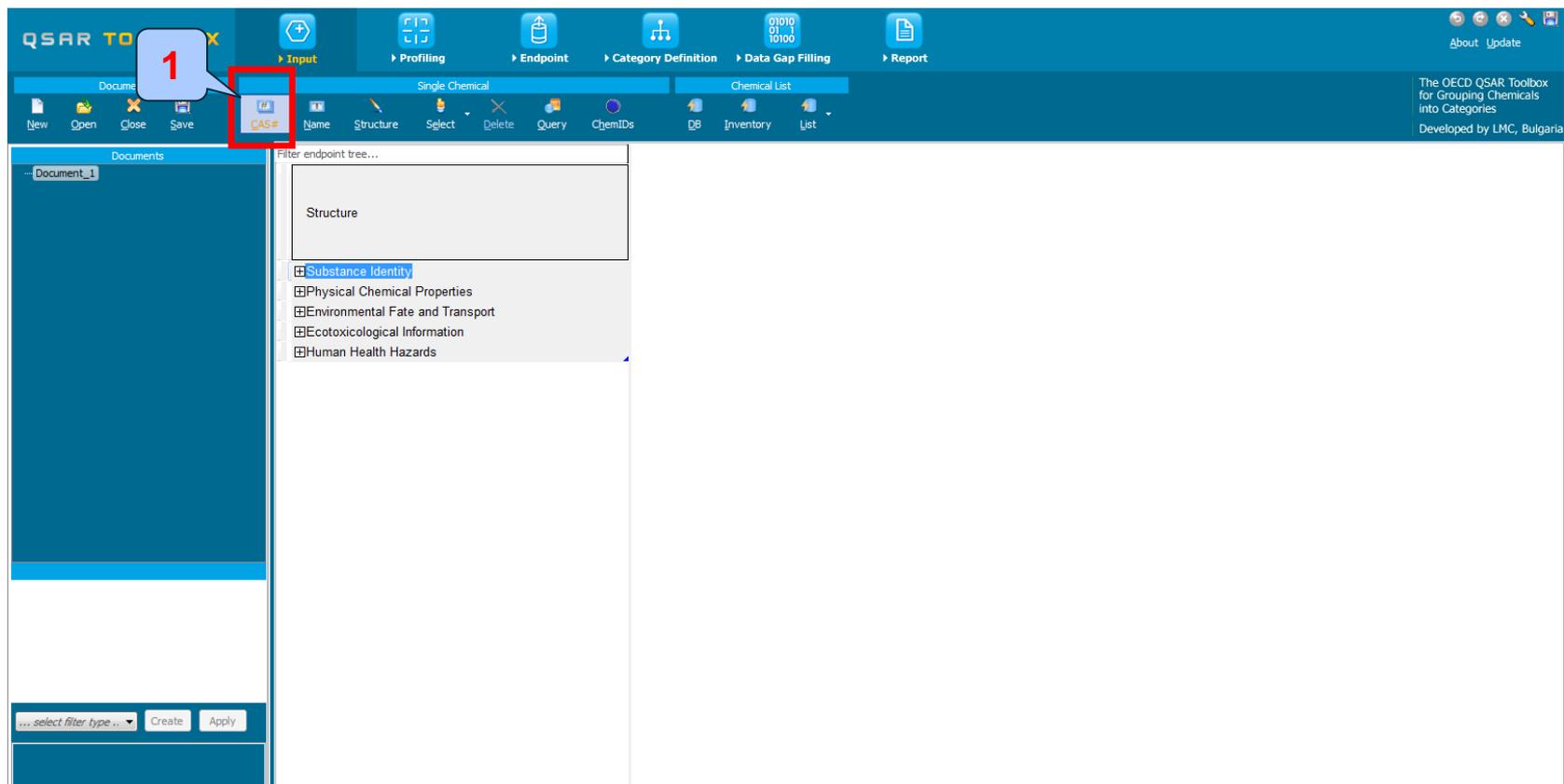
- Chemical Name
- Chemical Abstract Services (CAS) number (#)
- SMILES (simplified molecular information line entry system) notation/InChi
- Drawing chemical structure
- Select from User List/Inventory/Databases
- Chemical IDs such as EC number, Einecs number

B. Group of chemicals

- User List/Inventory
- Specialized Databases

Chemical Input Screen

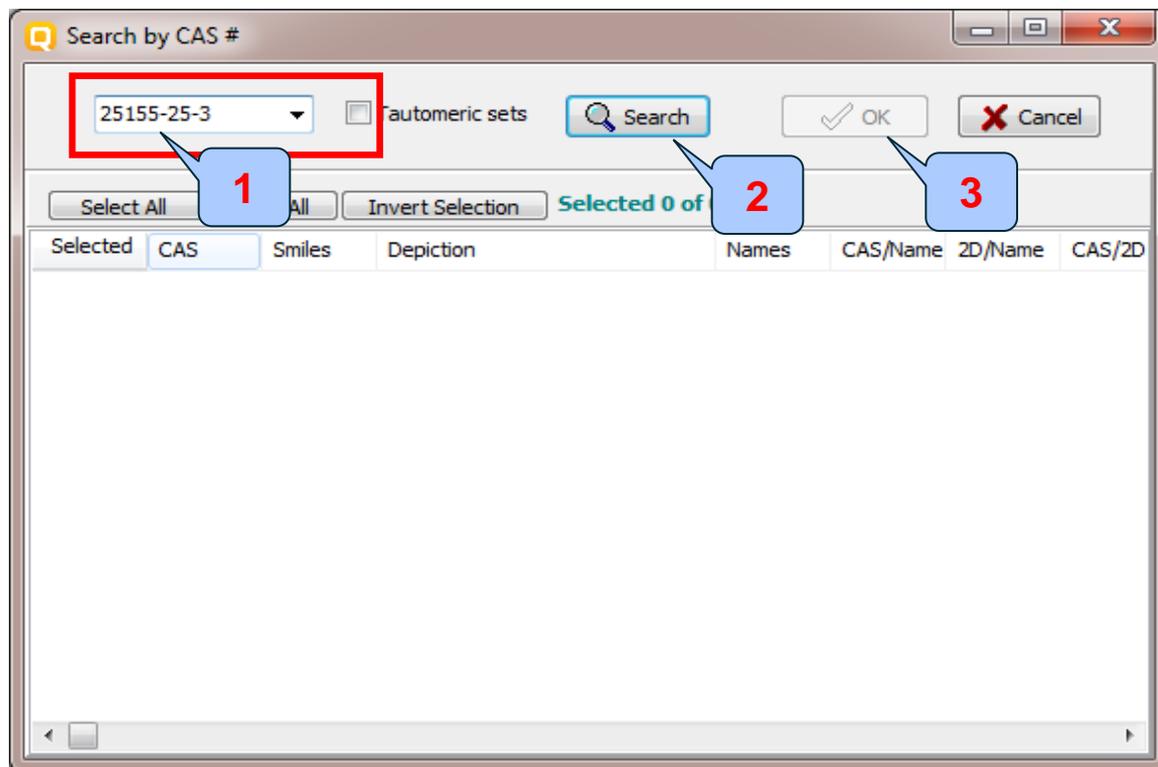
Input target chemical by CAS#



1. Click on CAS#

Chemical Input Screen

Enter CAS# 25155-25-3



1. **Enter** the CAS# In the 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.

Search by CAS #

25155-25-3 Tautomeric sets

Select All Clear All Invert Selection Selected 2 of 2

| Selected | CAS | Smiles | Depiction | Names | CAS/Name | 2D/Name | CAS/2D |
|-----------|------------|----------------|-----------|--|--|---|---|
| 1. Yes | 25155-25-3 | CC(C)(C)OOC(C) | | 1: bis(tert-b 2: peroxide, 3: [1,3(or 1, 4: 1,4-bis[2- 5: peroxide, 6: 1,4-bis(al 7: reaction r 8: peroxide | 1:: Moderate Quali 1:: Bacterial mu 2:: Genotoxicity 3:: METI Japan 4:: US HPV Cha 5:: USER DEFIN 2:: High Quality 1:: Canada DSL | 1:: Low Quality 1:: USER DEFINED 2:: Genotoxicity O 3:: Bacterial muta 2:: High Quality 1:: TSCA 2:: Canada DSL 3:: DSSTOX | : High Quality 1:: Bacterial 2:: Canada I 3:: DSSTOX 4:: ECHA CH 5:: ECHA PF 6:: EINECS 7:: Genoxi |
| 2. Yes | 25155-25-3 | CC(C)(C)OOC(C) | | 1: bis(tert-b | 1:: Moderate Quali 1:: Bacterial mu 2:: Genotoxicity 3:: METI Japan 4:: US HPV Cha 5:: USER DEFIN | 1:: Low Quality 1:: US HPV Challe 2:: METI Japan | : Low Quality, Conf 1:: METI Jap 2:: US HPV C |



In case a structure has several CAS numbers or a structure could be related to more than one substance, more than one chemical identity could be retrieved. In this case the user can decide which substance is to be retained for the subsequent workflow.

Chemical Input

Target chemical identity

The screenshot shows the QSAR Toolbox software interface. The main workspace is divided into several sections. On the left, there is a 'Documents' panel showing a document named 'Document_1' with CAS number 25155-25-3. The main workspace is divided into two columns: '1 [target]' and '2 [target]'. The 'Substance Identity' section is expanded, showing the following information:

| Field | 1 [target] | 2 [target] |
|--------------------|---|-------------------------|
| CAS Number | 25155-25-3 | 25155-25-3 |
| EINECS | 2466783 | NA |
| Chemical Name | bis(tert-butyl)dioxy... peroxide, [1,3(or 1,... [1,3(or 1,4)-phenyl... 1,4-bis[2-(tert-butyl... peroxide, [1,3(or 1,... 1,4-bis(alpha-(t-but... reaction mass of 1... | bis(tert-butyl)dioxy... |
| Molecular Formula | C20H34O4 | C20H34O4 |
| Structural Formula | CC(C)(C)OOC(C)(... | CC(C)(C)OOC(C)... |

A red circle highlights the 'Substance Identity' section, and a blue callout box with the number '1' points to it.

1. Double click "Substance Identity"; this displays the chemical identification information.
Note that existing names of the target chemical are in different colours (see next screen shot).

Chemical Input

Target chemical identity

1

1. The chemical with high quality assurance (QA) relation is selected for further read-across analysis

Chemical Input

Chemical identity

The colour code indicates the reliability of the chemical identifier:

- **Green:** There is a high consistency 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
- The exercise
- **Workflow**
 - Chemical 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

Summary information of the different profilers are provided in the "About"

The screenshot shows the QSAR Toolbox software interface. The top navigation bar includes 'Input', 'Profiling', 'Endpoint', 'Category Definition', and 'Data Gap Filling'. The Profiling side-bar lists various methods, with 'Protein binding alerts for skin sensitization by OASIS v1.4' selected. The 'About' window provides details for this profiler, including its name, short description, disclaimer, donor, author, website, version, and relevance to endpoints. A red arrow points from the 'Documentation' button in the side-bar to the 'About' window.

| About section of a profiler | |
|---|--|
| Name of the profiler | Protein binding alerts for skin sensitization v1.4 |
| Developer; Donator; date; version | |
| Developer: | Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria, |
| Donator: | L'Oréal, ExxonMobil, Procter & Gamble, Unilever, Research Institute for Fragrance Materials (RIFM), Dow Chemical, Danish National Food Institute, Denmark |
| Version 1.4 | July 2016 |
| Relevance/Applicability to endpoint(s) | This profiler has been developed by industry consortia involving ExxonMobile, Procter&Gamble, Unilever, Research Institute for Fragrance Materials (RIFM), Dow and Danish National Food Institute with the Laboratory of Mathematical Chemistry and the partnership of Dr D.Roberts, as a part of the TIMES model for predicting skin sensitization. The profiler is intended to be used for the assessment of protein binding interaction of chemicals and especially interaction with skin proteins. The profiler has been developed based on mechanistic knowledge for skin sensitisation of dataset of 875 chemicals tested by Local Lymph Node Assay (LLNA), Guinea Pig Maximization Test (GPMT) and chemicals from the BfR list. A list of 100 structural alerts has been derived, based on the mechanistic knowledge of training set chemicals. The list of 102 structural alerts has been separated into 10 mechanistic domains. Each of the mechanistic domains has been separated into |

- 1. Select** the name of the profiler, perform right click on it and then
- 2. Select** About
- Detailed documentation is available within **"Documentation"** button
- 4. Close** before proceeding

Profiling Overview

- Short description of the profilers is available within the About
- Details of the boundaries coded the rules of the categories along with textual description for each category is available within “View” functionality (shown on the next slide)

Profiling Side-Bar to Profiling

1. Highlight the profiler

2. Click View

Protein binding alerts for skin sensitization by OASIS v1.4

Mechanistic Domain: Radical

Mechanistic Alert: Free Radical formation

Structural Alert: Generated free radicals

The chemicals are strong sensitizers as a result of Free radical reactions on proteins:

- c1ccc(cc1)N=NH → c1ccc(cc1)[C] + N#N → c1ccc(cc1)Pr
- O=S(=O)(Cl)N(A) → O=S(=O)([N+])N(A) → O=S(=O)(Pr)N(A)

A = H, Na
- Xc1cc(O)c(X)c(X)c1R → Xc1cc(O)c(X)c(X)c1R[O] → Xc1cc(O)c(X)c(X)c1RPr

X = Cl, Br, I or NO₂
R = S or amido

Profiling

Profiling the target chemical

- The outcome of the profiling determines the most appropriate way to search for analogues (detailed information in Manual for getting started (Chapter 4). <http://www.oecd.org/dataoecd/58/56/46210452.pdf>
- Table 4 - 1 in chapter 4 (Manual for getting started) lists a selection of profilers and their relevance for different endpoints of regulatory relevance.
- For example the following mechanistic/endpoint specific profiling schemes are relevant to the Skin sensitization endpoint:
 - Protein binding by OASIS v.1.4 – mechanistic grouping
 - Protein binding by OECD – mechanistic grouping
 - Protein Binding Potency – mechanistic grouping
 - Protein binding alerts for skin sensitization by OASIS v1.4 – endpoint specific

Profiling

Profiling the target chemical

The screenshot shows the QSAR Toolbox software interface. The main window displays a chemical structure and a list of endpoints. The 'Profiling Schemes' dialog box is open, showing a list of profiling methods. The 'Apply' button is circled in red and labeled '2'. The 'General Mechanistic' section is expanded, and all checkboxes are checked, labeled '1'. The main window shows a chemical structure and a list of endpoints.

1. Check all the profilers.
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 profiling result based on US-EPA profiler
- This result will be used to search for suitable analogues in the next steps of the exercise.

Profiling

Profiling the target chemical

1. Right click over the profiling result to review it.

Outlook

- Background
- The exercise
- **Workflow**
 - Chemical 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 Gather data

The screenshot shows the QSAR Toolbox 3.4.0.17 interface. The 'Gather' button in the top menu is circled in red and labeled with a '3'. The 'Human Health Hazards' section in the left tree is expanded, with 'Skin sensitization' and 'Skin sensitization ECETOC' selected, labeled with a '2'. The 'Filter endpoint tree...' window shows a target endpoint '1 [target]' with its chemical structure and associated identifiers like CAS Number (25155-25-3) and EINECS (2466783), labeled with a '1'.

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

- 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).

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, an insert window appears stating there was “no data found” for the target chemical (see next screen shot).

Endpoint Gather data

The screenshot displays the QSAR Toolbox 3.4.0.17 interface. The 'Endpoint' menu is active, showing options like 'Gather', 'Import', 'Export', 'Delete', and 'Tautomerize'. An 'Information' dialog box is open in the center, with the message: "There are no experimental data available for the chemicals of interest." An arrow points to the 'OK' button in the dialog box.

Information

There are no experimental data available for the chemicals of interest.

OK

Close the inserted window by **Clicking** on "OK"

Recap

- In module one, you have entered the target chemical being sure of the correct structure.
- In the second module, you have profiled the target chemical.
- In the third module, you have found that no experimental data is currently available in the Toolbox for this structure.
- In other words, you have identified a data gap which you would like to fill.
- **Click** on “Category Definition” to move to the next module.

Outlook

- Background
- The exercise
- **Workflow**
 - Chemical Input
 - Profiling
 - Endpoint
 - **Category definition**

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 chemicals on the following link (Chapter 4).
<http://www.oecd.org/dataoecd/58/56/46210452.pdf>

Category Definition

Overview

- This module provides the user with several means of grouping chemicals into a toxicologically meaningful category that includes the target molecule.
- This is the critical step in the workflow.
- Several options are available in the Toolbox to assist the user in refining the category definition.

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 performed (endpoint dependant)
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**

Category Definition

Defining US-EPA New Chemical categories

1. Highlight the "US-EPA New Chemical Categories"

2. Click Define

3. Click OK to confirm the defined category for the target chemical

4. Click OK

1. **Highlight** the "US-EPA New Chemical Categories" 2. **Click** Define
 3. **Click** OK to confirm the defined category for the target chemical 4. **Click** OK

Category Definition

Defining US-EPA New Chemical categories

Due to overlap between the Toolbox databases for intersecting chemicals the same data may be found simultaneously. Data redundancies are identified and the user has the opportunity to select either a single data value or all data values.

Repeated values for: 3 data-points, 1 groups, 1 chemicals

Data points...

| | Endpoint | CAS | Structure | Value | |
|-------------------------------------|----------|---------|---|-----------------|---------------|
| <input checked="" type="checkbox"/> | S W A N | 79-21-0 |  | Not sensitising | Miscellaneous |
| <input checked="" type="checkbox"/> | S W A N | 79-21-0 | | Not sensitising | Miscellaneous |
| <input checked="" type="checkbox"/> | S W A N | 79-21-0 | | Not sensitising | Miscellaneous |

1

Select one

Invert

Check All

Uncheck All

2

OK

Cancel

1. Click **Select one**
2. **OK** to retrieve all available experimental data

Category Definition

Defining US-EPA New Chemical categories

The experimental results for the analogues appeared on datamatrix

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Categorize Delete

Define Define with metabolism Subcategorize Combine Clustering Delete Delete All

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

Grouping methods

- Predefined
 - Database Affiliation
 - Inventory Affiliation
 - OECD HPV Chemical Categories
 - Substance Type
 - US-EPA New Chemical Categories
- General Mechanistic
 - Biodeg BioHC half-life (Biowin)
 - Biodeg primary (Biowin 4)
 - Biodeg probability (Biowin 1)
 - Biodeg probability (Biowin 2)
 - Biodeg probability (Biowin 5)
 - Biodeg probability (Biowin 6)
 - Biodeg probability (Biowin 7)
 - Biodeg ultimate (Biowin 3)
 - DNA binding by OASIS v.1.4
 - DNA binding by OECD
 - DPRA Cysteine peptide depletion
 - DPRA Lysine peptide depletion
 - Estrogen Receptor Binding
 - Hydrolysis half-life (ka, pH 7)(Hydrowin)
 - Hydrolysis half-life (ka, pH 8)(Hydrowin)
 - Hydrolysis half-life (kb, pH 7)(Hydrowin)
 - Hydrolysis half-life (kb, pH 8)(Hydrowin)
 - Hydrolysis half-life (pH 6.5-7.4)
 - Ionization at pH = 1
 - Ionization at pH = 4
 - Ionization at pH = 7.4
 - Ionization at pH = 9
 - Protein binding by OASIS v1.4
 - Protein binding by OECD
 - Protein binding potency

Defined Categories

- Document_2
 - [12] Peroxides (US-EPA New Chemical Categories)

Filter endpoint tree...

Structure

Human Health Hazards

- Acute Toxicity
- Bioaccumulation
- Carcinogenicity
- Developmental Toxicity / Teratogenicity
- Genetic Toxicity
- Immunotoxicity
- Irritation / Corrosion
- Neurotoxicity
- Photoinduced Toxicity
- Repeated Dose Toxicity
- Sensitisation
 - Skin
 - In Chemico
 - In Vitro
 - In Vivo
 - GPMT (8/8) M: Positive M: Positive M: Positive
 - HR IPT
 - LLNA (1/1) M: Positive M: Positive M: Negative
 - Miscellaneous (3/3) M: Negative M: Positive M: Negative
 - Undefined Assay
- ToxCast
- Toxicity to Reproduction

| Endpoint | 1 [target] | 2 | 3 | 4 | 5 | 6 | 7 |
|---------------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|
| GPMT (8/8) | | | | | M: Positive | M: Positive | M: Positive |
| LLNA (1/1) | | | | M: Positive | M: Positive | | |
| Miscellaneous (3/3) | | M: Negative | M: Positive | M: Negative | | | |

1. Chemical statistics presenting the number of chemicals and the available experimental data.

Outlook

- Background
- The exercise
- **Workflow**
 - Chemical Input
 - Profiling
 - Endpoint
 - Category definition
 - **Data Gap Filling**

Data Gap Filling Overview

- “Data Gap Filling” module gives access to three different data gap filling tools:
 - Read-across
 - Trend analysis
 - Q)SAR models
- Depending on the situation, the most relevant data gap mechanism should be chosen, taking into account the following considerations:
 - Read-across is the appropriate data-gap filling method for “qualitative” endpoints like skin sensitisation or mutagenicity for which a limited number of results are possible (e.g. positive, negative, equivocal). Furthermore read-across is recommended for “quantitative endpoints” (e.g., 96h-LC50 for fish) if only a low number of analogues with experimental results are identified.
 - Trend analysis is the appropriate data-gap filling method for “quantitative endpoints” (e.g., 96h-LC50 for fish) if a high number of analogues with experimental results are identified.
 - “(Q)SAR models” can be used to fill a data gap if no adequate analogues are found for a target chemical.
- In this example, we apply read-across.

Data Gap Filling

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*).
- In order to unify the different skin sensitization potential values grouped in two or three different values (negative; weak sensitizer; strong sensitizer) the scale definitions and respectively scale conversions have been developed
- The default scale for Skin Sensitisation is “Skin Sensitisation ECETOC”. It converts all skin data into: Positive, Negative, and Equivocal.

Data Gap Filling

Apply Read across

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR BOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Filter endpoint tree...

Structure

Substance Identity
 Physical Chemical Properties
 Environmental Fate and Transport
 Ecotoxicological Information
 Human Health Hazards
 Acute Toxicity
 Bioaccumulation
 Carcinogenicity
 Developmental Toxicity / Teratogenicity
 Genetic Toxicity
 Immunotoxicity
 Irritation / Corrosion
 Neurotoxicity
 Photoinduced Toxicity
 Repeated Dose Toxicity
 Sensitisation
 Skin
 In Chemico
 In Vitro
 In Vivo
 Undefined Type of Method
 ToxCast
 Toxicity to Reproduction

| | | | | | | |
|------------|-------------|-----------------------|-------------|-------------|-------------|----|
| 1 [target] | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |
| (11/12) | M: Negative | M: Positive, Positive | M: Negative | M: Positive | M: Positive | M: |

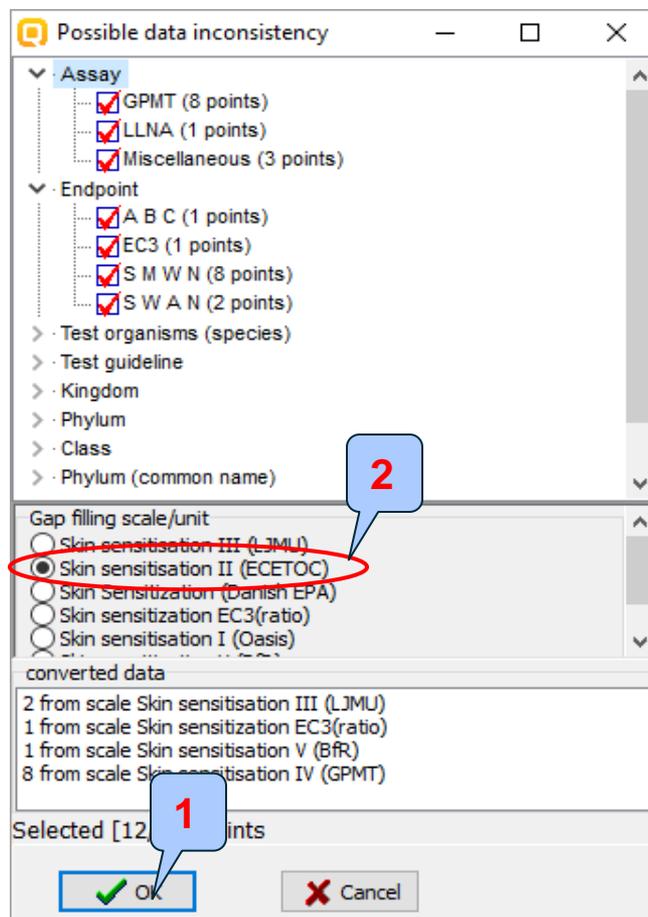
Read-across
 Trend analysis
 (Q)SAR models

Target Endpoint

Human Health Hazards Sensitisation Skin In Vivo

1. Click on the cell corresponding to "In vivo" data. 2. Select Read-across 3. Click Apply

Data Gap Filling Scale definition

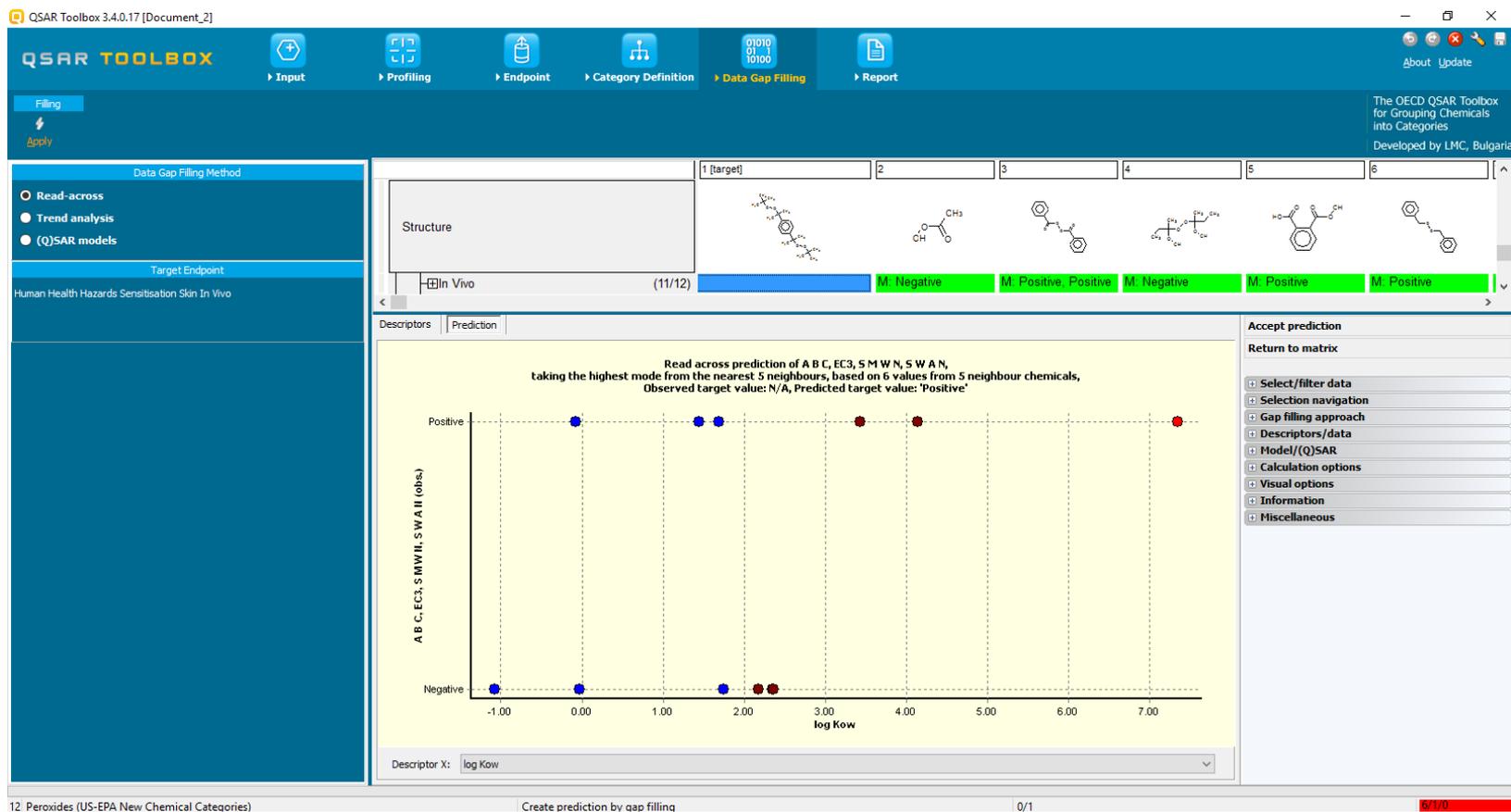


1. Click OK

2. Scale Skin sensitisation II(ECETOC) is selected by default as being default scale

Data Gap Filling 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).



Data Gap Filling 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).

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

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

Structure

In Vivo (11/12)

M: Negative M: Positive, Positive M: Negative M: Positive M: Positive

Descriptors Prediction

Read across prediction of A B C, EC3, S M W N, S W A 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: 'Negative'

Positive

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

6.00 7.00

Accept prediction

Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Data usage

Prediction approach options

- Visual options
- Information
- Miscellaneous

Set usage of data per chemical:

- All
- Minimal
- Maximal
- Lower median
- Higher median
- Mode(s)
- Lowest mode
- Highest mode

OK

Worst case scenario is applied. Follow the steps:

1. **Select** Calculation options
2. **Click** on the "Data usage".
3. **Select** "Maximal"
4. **OK**

Data Gap Filling

Subcategorization by US-EPA New Chemical Categories

The screenshot displays the QSAR Toolbox interface during a subcategorization task. On the left, the 'Subcategorization' window is open, showing a list of predefined categories. 'US-EPA New Chemical Categories' is highlighted with a red box and a callout '2'. The main window shows the 'Data Gap Filling' tab. The 'Structure' field contains '(11) Peroxides', and a list of chemical structures is displayed below it. A scatter plot shows the relationship between 'log Kow' (x-axis) and 'log Kow' (y-axis), with points colored by prediction (M. Negative, M. Positive). A callout '1' points to the 'Subcategorize' button in the 'Accept prediction' panel. A callout '3' points to the 'Remove' button at the bottom of the 'Subcategorization' window.

1. Click Subcategorize in order to refine the category (phase I, slide 34, 35)
2. Select US-EPA New Chemical Categories
3. Click Remove to eliminate dissimilar chemicals.

Data Gap Filling

Subcategorization by Protein binding alerts for skin sensitization by OASIS v1.4

The screenshot displays the QSAR Toolbox interface during a subcategorization task. The left sidebar lists various endpoint-specific methods, with 'Protein binding alerts for skin sensitization by OASIS v1.4' highlighted in a red box and labeled with a '2'. The central workspace shows a chemical structure and a prediction matrix with columns for different descriptors and rows for different chemicals. A callout box labeled '1' points to the 'Subcategorize' button in the right sidebar. Another callout box labeled '3' points to the 'Remove' button at the bottom of the workspace. The prediction matrix shows a 'Read across prediction of A B C, EC3, S M W N, S W A 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: 'Negative''.

1. Click Subcategorize.
2. Select Protein binding alerts for skin sensitization by OASIS v1.4.
3. Click Remove to eliminate dissimilar chemicals.

Data Gap Filling

Results after subcategorization

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

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

Read across prediction of ABC, EC3, SMWN, SWA II, 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: 'Negative'

Structure

In Vivo (7/7)

M. Negative M. Positive M. Positive M. Positive M. Negative

Descriptors Prediction

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

Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR

Calculation options
Data usage
Prediction approach options

Visual options
Information
Miscellaneous

All analogues have peroxide group, but they are quite dissimilar. In this respect we are selecting ECHA CHEM database in order to expand the category of analogues and to identify more suitable analogues for the current read-across analysis.

Data Gap Filling

Interpreting Read-across

- In this example, all analogues have peroxide group, but they are very structurally dissimilar
- The prediction is not reliable due to the structurally dissimilar analogues and could not be accepted
- In order to expand the category of analogues and identify more similar analogues to the target chemical, data extracted from ECHA Chem database is used in the further read-across analysis (see next screen shots).

Data Gap Filling

Return to the matrix

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

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

Read across prediction of A B C, E C 3, S M W N, S W A 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: '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

Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR

Calculation options
Data usage
Prediction approach options

Visual options
Information
Miscellaneous

1. Select Return to matrix

Endpoint

Gather data from ECHA Chem database

1. Go to the Endpoint

2. Expand the Human Health Hazards section

3. Select ECHA CHEM database

4. Click Gather

Endpoint

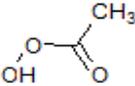
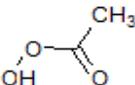
Gather data

- Toxicity information on the target chemical is electronically collected from the selected dataset(s).
- It should be kept in mind that ECHA CHEM database has been selected
- In this case there is experimental data extracted for the target chemical (see next screen shot).

Endpoint Gather data

Repeated values for: 28 data-points, 11 groups, 5 chemicals

Data points...

| | Endpoint | CAS | Structure | Value | Any other informat |
|-------------------------------------|---------------|---------|---|-----------|---|
| <input checked="" type="checkbox"/> | | 79-21-0 | | corrosive | |
| <input checked="" type="checkbox"/> | | 79-21-0 | | corrosive | |
| <input checked="" type="checkbox"/> | | 79-21-0 |  | corrosive | <html> <head> </head> <body> <pre> <p style="margin-bott 35.25pt;left:35.25 |
| <input checked="" type="checkbox"/> | gene mutation | 79-21-0 |  | negative | <html> <head> </head> <body> <p style="top:0;marg |

1. Select one

2. Click OK

Endpoint Gather data

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Data Import Export Delete Tautomerize

Gather Import IUCLIDS Export IUCLIDS Database Inventory Database

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

Select All Unselect All Invert About

Human Health Hazards

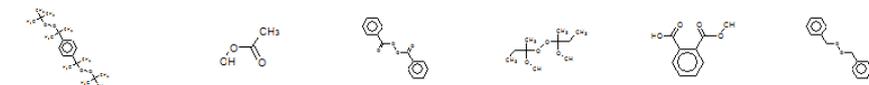
- Acute Oral Toxicity database (ChemIDPlus)
- Bacterial mutagenicity ISSSTY
- Carcinogenic Potency Database (CPDB)
- Carcinogenicity & mutagenicity ISSCAN
- Cell Transformation Assay ISSCTA
- Dendritic cells COLIPA
- Developmental & Reproductive Toxicity (DART)
- Developmental toxicity ILSI
- ECHA CHEM
- ECOTOX
- Estrogen Receptor Binding Affinity OASIS
- Eye Irritation ECETOC
- Genotoxicity OASIS
- Human Half-Life
- Keratinocyte gene expression Givaudan
- Keratinocyte gene expression LuSens
- Micronucleus ISSMIC
- Micronucleus OASIS
- MUNEQ non-cancer EFSA
- Rep Dose Tox Fraunhofer ITEM
- Repeated Dose Toxicity HESS
- Rodent Inhalation Toxicity Database
- Skin Irritation
- Skin sensitization
- Skin sensitization ECETOC

Select All Unselect All Invert About

Canada DSL
COSING
DSSTOX
ECHA PR
EINECS
HPVC OECD
METI Japan

Filter endpoint tree... 1 [target] 2 3 4 5 6

Structure



| | | | | | | | |
|---|--------|---------------------------------------|------------------------|---------------------------|------------------------|-------------|-------------|
| Developmental Toxicity / Teratogenicity | (2/6) | M: 300 mg/kg bw/day (actua... | M: 30.4 mg/kg per... | | | | |
| Genetic Toxicity | (4/20) | M: negative, negative, negative | M: negative, negati... | M: negative, negati... | M: negative, negati... | | |
| Irritation / Corrosion | (4/12) | M: not irritating, slightly irrita... | M: corrosive, corro... | M: not irritating, sli... | M: corrosive, corro... | | |
| Repeated Dose Toxicity | (4/19) | M: 200 mg/kg bw/day (actua... | M: 23.4 mg/kg bw/... | M: 500 mg/kg bw/... | M: 200 mg/kg bw/... | | |
| Sensitisation | | | | | | | |
| Skin | | | | | | | |
| In Vivo | | | | | | | |
| Buehler Test | (2/2) | | M: not sensitising | M: sensitising | | | |
| GPMT | (8/8) | | | | | M: positive | M: Positive |
| Guinea Pig Maximisation Test | (2/2) | | M: not sensitising | | M: not sensitising | | |
| HRIP | | | | | | | |
| LLNA | (1/1) | | | M: Positive | | | |
| Miscellaneous | (3/3) | | M: Negative | M: Positive | M: Negative | | |
| Mouse Local Lymphnode Assay (LL...) | (2/2) | M: not sensitising | | M: sensitising | | | |
| Undefined Assay | | | | | | | |
| Undefined Type of Method | (1/1) | | | M: sensitising | | | |
| ToxCast | | | | | | | |
| Toxicity to Reproduction | (3/8) | M: 300 mg/kg bw/day (actua... | | M: 1E3 mg/kg bw/... | M: 75 mg/kg bw/d... | | |

1

1. Chemical statistics presenting the number of chemicals and the available experimental data.

Endpoint Gather data

QSAR Toolbox 3.4.0.17 [Document_2]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Data Import Export Delete Tautomerize

Gather Import IUCLID5 Export IUCLID5 Database Inventory Database

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

Databases

Select All Unselect All Invert About

Human Health Hazards

- Acute Oral Toxicity database (ChemIDPlus)
- Bacterial mutagenicity ISSSTY
- Carcinogenic Potency Database (CPDB)
- Carcinogenicity&mutagenicity ISSCAN
- Cell Transformation Assay ISSCTA
- Dendritic cells COLIPA
- Developmental & Reproductive Toxicity (DART)
- Developmental toxicity ILSI
- ECHA CHEM
- ECOTOX
- Estrogen
- Eye
- Genotoxicity
- Human Health
- Key
- Key
- Micro
- Micro
- ML
- Re
- Re
- Ro
- Skin
- Skin
- Transpose

Filter endpoint tree... 1 [target] 2 3 4 5 6

Structure

Developmental Toxicity / Teratogenicity (2/6) M: 300 mg/kg bw/day (actua... M: 30.4 mg/kg per...
Genetic Toxicity (4/20) M: negative, negative, negative M: negative, negati... M: negative, negati... M: negative, negati...
Immunotoxicity
Irritation / Corrosion (4/12) M: not irritating, slightly irrita... M: corrosive, corro... M: not irritating, sli... M: corrosive, corro...

| Endpoint | Value | Original value | Strain | Organ | Substance type | Study result type | Qualifier of guideline | Reference type | Reliability | Type of method | URL | Year | Test organisms (species) | Test guideline |
|--------------------|---|---|--------|-------|-----------------------------|---------------------|------------------------|----------------|----------------------------------|----------------|---|------|--------------------------|---|
| Skin Sensitisation | not sensitising (HT Version 20120101 phrasegroup_T21) | not sensitising (HT Version 20120101 phrasegroup_T21) | CBA | Skin | multi constituent substance | experimental result | according to | study report | 1 (reliable without restriction) | in vivo | http://echa.europa.eu/scripts/redirects/rs_redirect.asp?uid=AGGR-180-51-cb-02-c2-4463-b5d0-5b2bd32b60bd% | 2010 | mouse | OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay) |

Inventories

Select All Unselect All Invert About

- Canada DSL
- COSING
- DSSTOX
- ECHA PR
- EINECS
- HPVC OECD
- METI Japan
- NICHAS

LLNA (1/1) M: Positive
Miscellaneous (2/2) M: Positive M: Negative
Mouse Local Lymphnode Assay (LLNA) (2/2) M: not sensitising
Undefined Assay
Undefined Type of Method (1/1) M: sensitising
ToxCast
Toxicity to Reproduction (3/8) M: 300 mg/kg bw/day (actua... M: 1E3 mg/kg bw/... M: 75 mg/kg bw/...

1

1. There are negative skin data (LLNA) for the target chemical extracted from ECHA CHEM database. We will try to reproduce it.

Expand the defined category

- The next step of the exercise is to identify new analogues. The procedure of defining the category should be repeated in a same manner because the software should search for analogues within the newly selected ECHA CHEM database

Category Definition

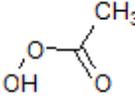
Defining US-EPA New Chemical categories

1. **Highlight** the "US-EPA New Chemical Categories" 2. **Click** Define
 3. **Click** OK to confirm the defined category for the target chemical 4. The software identify 53 analogues **Click** OK

Endpoint Gather data

Repeated values for: 210 data-points, 89 groups, 79 chemicals

Data points...

| | Endpoint | CAS | Structure | Value | Any other informat |
|-------------------------------------|----------|-----------|--|----------------|--|
| <input checked="" type="checkbox"/> | | 79-21-0 | | corrosive | |
| <input checked="" type="checkbox"/> | | 79-21-0 | | corrosive | |
| <input checked="" type="checkbox"/> | | 79-21-0 |  | corrosive | <html> <head> </head> <body> <pre> <p style="margin-bot 35.25pt;left:35.25 |
| | | 3006-82-4 | | not irritating | <html> |

Buttons: Select one, Invert, Check All, Unchecked, (with callout 2), (with callout X)

1. Select one
2. Click OK

Data Gap Filling

Apply Read across

QSAR Toolbox 3.4.0.17 [Document_1]

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

Filter endpoint tree... [1 [target]] 2 3 4 5 6 7 8

Structure

Read-across Trend analysis (Q)SAR models

Target Endpoint: Human Health Hazards Sensitisation Skin In Vivo

| Endpoint | 1 [target] | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---------------------------|-------------------------|-------------------------|------------------------|--------------------------|-------------------------|---------------------------|----|
| Acute Toxicity (43/233) | M: >2E3 mg/kg | M: 1.39 mL/kg bw,... | M: 560 mg/kg, 440... | M: 2.54E3 mg/kg, ... | M: >2E3 mg/kg, >... | M: 2E3 mg/kg, 3.3... | M: >5E3 mg/kg, 1... | M: |
| Bioaccumulation | | | | | | | | |
| Carcinogenicity (2/3) | | | | | | | M: no effects, no data | |
| Developmental Toxicity / Teratogenicity (14/36) | M: 300 mg/kg bw/... | | M: 35 mg/kg bw/d... | M: 30.4 mg/kg per... | M: ≈300 mg/kg bw... | M: 300 mg/kg bw/... | | M: |
| Genetic Toxicity (44/193) | M: negative, negati... | M: positive, positiv... | M: positive, positiv... | M: negative, negati... | M: negative, negati... | M: negative, positiv... | M: negative, negati... | M: |
| Immunotoxicity | | | | | | | | |
| Irritation / Corrosion (43/113) | M: not irritating, sli... | M: NOT_SPECIFI... | M: corrosive, slight... | M: corrosive, corro... | M: not irritating, no... | M: Category 2 (irit... | M: not irritating, sli... | M: |
| Neurotoxicity | | | | | | | | |
| Photoinduced Toxicity | | | | | | | | |
| Repeated Dose Toxicity (36/96) | M: 200 mg/kg bw/... | M: 1.39 mg/m³ air | M: 2.1 mg/kg bw/d... | M: 23.4 mg/kg bw/... | M: 100 mg/kg bw/... | M: ≈30 mg/kg bw/... | M: 500 mg/kg bw/... | M: |
| Sensitisation | | | | | | | | |
| Skin | | | | | | | | |
| In Chemico | | | | | | | | |
| In Vitro | | | | | | | | |
| In Vivo | | | | | | | | |
| Buehler Test (7/7) | | | | M: not sensitising | M: not sensitising | M: not sensitising | M: sensitising | |
| GPMT (8/8) | | | | | | | | |
| Guinea Pig Maximisation Test (22/22) | | | M: sensitising | M: not sensitising | | | | |
| HRIPT | | | | | | | | |
| LLNA (1/1) | | | | | | | M: Positive | |
| Miscellaneous (3/3) | | | | M: Negative | | | M: Positive | |
| Mouse Local Lymphnode Assay (LLNA) (12/12) | M: not sensitising | | | | | M: sensitising | M: sensitising | M: |
| Undefined Assay | | | | | | | | |
| Undefined Type of Method (1/1) | | | | | | | M: sensitising | |

54 Peroxid... 70

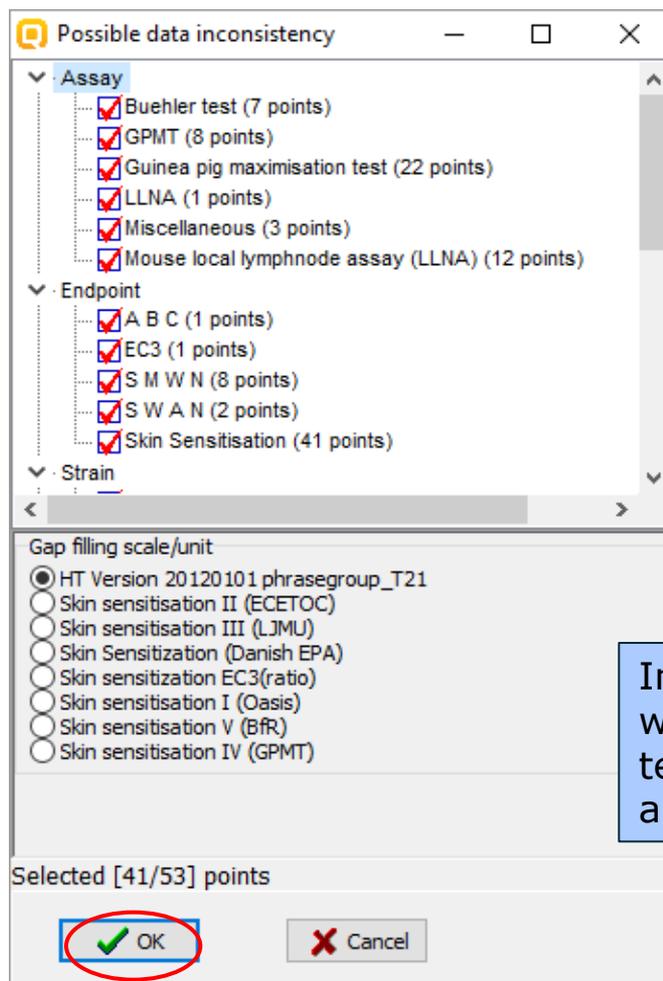
The OECD QSAR Toolbox for Grouping Chemicals into Categories

15.07.2016

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1. Click on the cell corresponding to "In Vivo" node for the target chemical.
2. Select Read-across
3. Click Apply

Data Gap Filling Read-across



In this case we are mixing data with different strain, species test type. In this exercise we are using "HT" scale.

Data Gap Filling Read-across

QSAR Toolbox 3.4.0.17 [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] 3 4 5 6 7 8 9

In Vivo (37/45) M. not sensitising M. sensitising M. not sensitising M. not sensitising M. sensitising, not M. sensitising, sen M. not sensitising M.

Descriptors Prediction

Accept prediction Return to matrix

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

Read across prediction of Skin Sensitisation, taking the mode from the nearest 5 neighbours, based on 5 values from 5 neighbour chemicals, Observed target value: 'not sensitising', Predicted target value: 'not sensitising'

Descriptor X: log Kow

54 Peroxides (US-EPA New Chemical Categories) Create prediction by gap filling 0/1 17/10

Data Gap Filling

Subcategorization by US-EPA New Chemical Categories

The screenshot displays the 'Subcategorization' window of the OECD QSAR Toolbox. The interface is divided into several sections:

- Predefined Methods (Left Sidebar):** A list of grouping methods is shown, with 'US-EPA New Chemical Categories' highlighted under the 'General Mechanistic' section. Callout 2 points to this selection.
- Main Workspace:** Shows a list of chemicals with their predicted skin sensitization status. Below this is a scatter plot titled 'Read across prediction of Skin Sensitisation, taking the mode from the nearest 5 neighbours, based on 5 values from 5 neighbour chemicals, Observed target value: 'not sensitising', Predicted target value: 'not sensitising''. The plot has 'ambiguously sensitising', 'sensitising', and 'slightly sensitising' on the y-axis and a numerical scale from 0.0 to 22.0 on the x-axis. Callout 1 points to the 'Subcategorize' button in the right-hand panel.
- Right-Hand Panel:** Contains various control options under 'Accept prediction' and 'Return to matrix', including 'Subcategorize', 'Mark chemicals by descriptor value', and 'Filter points by test conditions'. Callout 1 points to the 'Subcategorize' button.
- Bottom Panel:** Shows a list of selected chemicals (2/34/36) and a 'Remove' button. Callout 3 points to this button.

1. Click Subcategorize 2. Select US-EPA New Chemical Categories 3. Click Remove to eliminate dissimilar chemicals.

Data Gap Filling

Subcategorization by Protein binding by OASIS v1.4

The screenshot displays the 'Subcategorization' window in the QSAR Toolbox. The 'Grouping methods' list on the left includes 'Protein binding by OASIS v1.4', which is highlighted with a red box and a callout '2'. The 'Target' dropdown menu is also highlighted with a red circle. The main workspace shows a list of chemicals with their predicted skin sensitization status. A scatter plot titled 'Read across prediction of Skin Sensitisation' shows a distribution of points across 'not sensitising' and 'sensitising' categories. A callout box '1' points to the 'Subcategorize' button in the right-hand panel.

1. **Click** Subcategorize.
 2. **Select** general mechanistic profiler Protein binding alerts by OASIS v1.4. This profiler provides information for presence of alert responsible for protein binding interaction independent from a particular endpoint.
- Note** that the target and the chemicals within the category have a general mechanistic alert for Protein Binding interaction indicating that sub-categorization with an endpoint specific profiler could be more appropriate (see next slide).

Data Gap Filling

Subcategorization by Protein binding alerts for skin sensitization by OASIS v1.4

1 Click Subcategorize.

2 Select Protein binding alerts for skin sensitization by OASIS v1.4. This profiler provides more endpoint specific information for presence of protein binding alerts responsible for interaction that may cause skin sensitization effect.

3 Note that the target chemical has no protein binding alert related specifically for skin sensitisation and sub-categorization was performed eliminating dissimilar chemicals (Click Remove, step 3)

Data Gap Filling

Interpretation of Protein binding result obtained by both protein binding alerts related to Peroxides category

- Positive protein binding alert (Organic peroxides) has been found for the target chemical by general mechanistic "Protein binding by OASIS v1.4" profile
- No positive Protein binding alert has been found for the target chemical based on endpoint specific "Protein binding alerts for skin sensitization by OASIS v1.4" profile. The reason for this is that organic peroxide could interact with proteins without eliciting skin sensitization effect. Additional information for both protein binding profilers is provided on the next slide
- The obtained analogues after protein binding elimination were not very similar to the target chemical. In this respect subcategorization by OFG (US-EPA) is applied as next subcategorization step (see slide 67)

Description of general mechanistic and endpoint specific Protein binding by OASIS profilers

General mechanistic: Protein binding by OASIS

The protein binding alerts have been developed by industry consortia involving ExxonMobil, Procter&Gamble, Unilever, Research Institute for Fragrance Materials (RIFM), Dow and Danish National Food Institute with the Laboratory of Mathematical Chemistry, Bourgas and the partnership of Dr D.Roberts, as a part of the TIMES model to predict skin sensitization. The scope of the profiler is to investigate presence of alerts within target molecules responsible for interaction with proteins.

Endpoint specific: Protein binding alerts for skin sensitization by OASIS

The scope of this profiler is to investigate the presence of alerts within the target molecules responsible for interaction with proteins and especially with skin proteins. This profiler accounts for incapability of some chemicals having an alert to interact with skin due to electronic and steric factors. This is explicitly defined by inhibition masks associated with some alerts.

Data Gap Filling Subcategorization by OFG (US-EPA)

1. Click Subcategorize.

2. Select Organic functional group (US EPA)

3. Click Remove to eliminate dissimilar chemicals

Data Gap Filling Read-across

QSAR Toolbox 3.4.0.17 [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

Data Gap Filling Method

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

Target Endpoint

Human Health Hazards Sensitisation Skin In Vivo

Structure

1 [target] 5 8 10 25 40 42 44

In Vivo (8/8) M: not sensitising M: not sensitising M: not sensitising M: not sensitising M: not s M: slightly M: not sensitising M:

1

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

Read across prediction of Skin Sensitisation, taking the mode from the nearest 5 neighbours, based on 5 values from 5 neighbour chemicals, Observed target value: 'not sensitising', Predicted target value: 'not sensitising'

Descriptor X: log

1. Accept prediction and return to matrix

54 Peroxides (US-EPA New Chemical Categories)

1/1/0

Recap

- Read-across is the appropriate data-gap filling method for “qualitative” endpoints like skin sensitisation. All the tested chemicals in the category except two were not sensitizing, the negative prediction for the target chemical could be accepted.
- You are now ready to complete the final module and to download the report.
- **Click** on “Report” to proceed to the last module.

Outlook

- Background
- The exercise
- **Workflow**
 - Chemical Input
 - Profiling
 - Endpoint
 - Category definition
 - Data Gap Filling
 - **Report**

Report Overview

- Report module could generate report on any of predictions performed with the Toolbox.
- Report module contains predefined report templates as well as a template editor with which users can develop a user defined templates.
- The report can then be printed or saved in different formats.

Report

QSAR Toolbox 3.4.0.17 [Document_1]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Filling Apply

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

Data Gap Filling Method

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

Target Endpoint

Human Health Hazards Sensitisation Skin In Vivo

Filter endpoint tree...

- Structure
- Substance Identity
- Physical Chemical Properties
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards
 - Acute Toxicity
 - Bioaccumulation
 - Carcinogenicity
 - Developmental Toxicity / Teratogenicity
 - Genetic Toxicity
 - Immunotoxicity
 - Irritation / Corrosion
 - Neurotoxicity
 - Photoinduced Toxicity
 - Repeated Dose Toxicity
 - Sensitisation
 - Skin
 - In Chemico
 - In Vitro
 - In Vivo**
 - Undefined Type of Method
 - ToxCast
 - Toxicity to Reproduction

| 1 [target] | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|--|--------------------------|-------------------------|--------------------------|-------------------------|---------------------------|---------------------------|---------------------------|
| | | | | | | | |
| (43/233) M: >2E3 mg/kg | M: 1.39 mL/kg bw/... | M: 560 mg/kg, 440... | M: 2.54E3 mg/kg, ... | M: >2E3 mg/kg, >... | M: 2E3 mg/kg, 3.3... | M: >5E3 mg/kg, 1... | M: ≥2E3 mg/kg, 1... |
| (2/3) M: 300 mg/kg bw/... | | M: 35 mg/kg bw/d... | M: 30.4 mg/kg per... | M: ≈300 mg/kg bw... | M: 300 mg/kg bw/... | M: no effects, no data | M: 150 mg/kg bw/... |
| (44/193) M: negative, negati... | M: positive, positiv... | M: positive, positiv... | M: negative, negati... | M: negative, negati... | M: negative, positiv... | M: negative, negati... | M: neg... |
| (43/113) M: not irritating, sli... | M: irritative, slight... | M: corrosive, corro... | M: not irritating, no... | M: Category 2 (irrit... | M: not irritating, sli... | M: not irritating, sli... | M: not irritating, sli... |
| (36/9) M: 300 mg/kg bw/... | M: 23.4 mg/kg bw/... | M: 100 mg/kg bw/... | M: ≈30 mg/kg bw/... | M: 500 mg/kg bw/... | M: 80 mg/kg bw/... | | |
| (45/54) M: not sensitising R: not sensitising | M: sensitising | M: not sensitising,... | M: not sensitising | M: sensitising, not... | M: sensitising, sen... | M: not sensitising | M: not sensitising |
| (1/1) | | | | M: sensitising | | | |
| (18/41) M: 300 mg/kg bw/... | | M: 21 mg/kg bw/d... | | M: 100 mg/kg bw/... | M: 300 mg/kg bw/... | M: 1E3 mg/kg bw/... | |

54 Peroxides

1. Select prediction
2. Right Click and Select Report

Report

QSAR Toolbox 3.4.0.17 [Document_1]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Reports Repository

Create Print Close Save as Register Unregister Update Clone Design

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

Available data to report

- Predictions
- (Q)SARs
- Categories

Available report templates

- Standard (predefined)
 - QSAR Model Reporting Format (QMRF v.3.4)
 - QSAR Toolbox Category Report (CCRF v.3.)
 - QSAR Toolbox Prediction Report (TPRF v.3.)
- Custom (user defined)
 - Editable copy of QSAR Model Reporting Form
 - Editable copy of QSAR Toolbox Category Report
 - Editable copy of QSAR Toolbox Prediction Report

show only relevant templates

Prediction [1]

Prediction of Skin Sensitisation for bis(tert-butyl-dioxyisopropyl)benzene 3 / 24

QSAR Toolbox prediction based on read-across

Prediction of Skin Sensitisation for bis(tert-butyl-dioxyisopropyl)benzene

1

Summary

Toxicity of the target chemical (not sensitising) is predicted from category members using read-across based on 5 values (not sensitising x3, sensitising x1, slightly x1) from 5 nearest neighbours compared by prediction descriptors. Category members are single chemicals or mixtures and are selected based on the profile of the target chemical. Only chemicals having experimental data are listed in the category.

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

The data used for calculating the current prediction is taken from 7 experimental values selected from the following database(s):

- ECHA CHEM

Below is a summary table for endpoint & descriptor values for the target chemical and the category members.

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.

| | Endpoint(s) | Descriptor(s) |
|--|-----------------------|---------------|
| | Human Health Hazards; | log Kow |

54 Perox

1/0/0

1. Report for Skin Sensitization

Report

QSAR Toolbox 3.4.0.17 [Document_1]

Input Profiling Endpoint Category Definition Data Gap Filling Report

Reports Repository

Create Print Close Save as Register Unregister Update Clone Design

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

Available data to report

- Predictions
- (Q)SARs
- Categories

Available report templates

- Standard (predefined)
 - QSAR Model Reporting Format (QMRF v.3.4)
 - QSAR Toolbox Category Report (CCRF v.3.)
 - QSAR Toolbox Prediction Report (TPRF v.3.)
- Custom (user defined)
 - Editable copy of QSAR Model Reporting Form
 - Editable copy of QSAR Toolbox Category Report
 - Editable copy of QSAR Toolbox Prediction Report

Prediction [1]

j. Predicted value (model result): not sensitising

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

4.3. Applicability domain (OECD Principle 3):
The target chemical **FATES** within applicability domain (see Section 3.1.b for detailed description of the domain)

4.4. Uncertainty of the prediction (OECD Principle 4): *manually editable field*

1. Predicted value

2. Applicability domain

Report

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QSAR TOOLBOX

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Prediction [1]

Prediction of Skin Sensitisation for bis(tert-butylidioxyp)benzene

APPENDIX 1 - Category members

The 7 category members are reported in more detail

1

used for read-across

1. Cat. member No.1:

1.1. CAS number:
6731-36-8

1.2. Other regulatory numbers:
Not reported

1.3. Chemical name(s):
1,1-bis(tert-butylidioxyp)-3,3,5-trimethyl cyclohexane peroxide, 1,1'-(3,3,5-trimethylcyclohexylidene)bis[2-(1,1-dimethylethyl)peroxy]-3,3,5-trimethylcyclohexane peroxide, (3,3,5-trimethylcyclohexylidene)bis(1,1-dimethylethyl)di-tert-butylperoxy-3,3,5-trimethylcyclohexane p
1,1-bis(tert-butylidioxyp)-3,3,5-trimethylcyclohexane di-tert-butyl 3,3,5-trimethylcyclohexylidene diperoxide peroxide, (3,3,5-trimethylcyclohexylidene)bis(1,1-dimethylethyl)peroxide, (3,3,5-trimethylcyclohexylidene)bisXtert-butylperoxide, (3,3,5-trimethylcyclohexylidene)bisX(1,1-dimethylethyl)peroxide, (3,3,5-trimethylcyclohexylidene)bis[tert-butylperoxide, (3,3,5-trimethylcyclohexylidene)bis(1,1-dimethylethyl)

1.4. Structural formula:

1. Additional information for category members

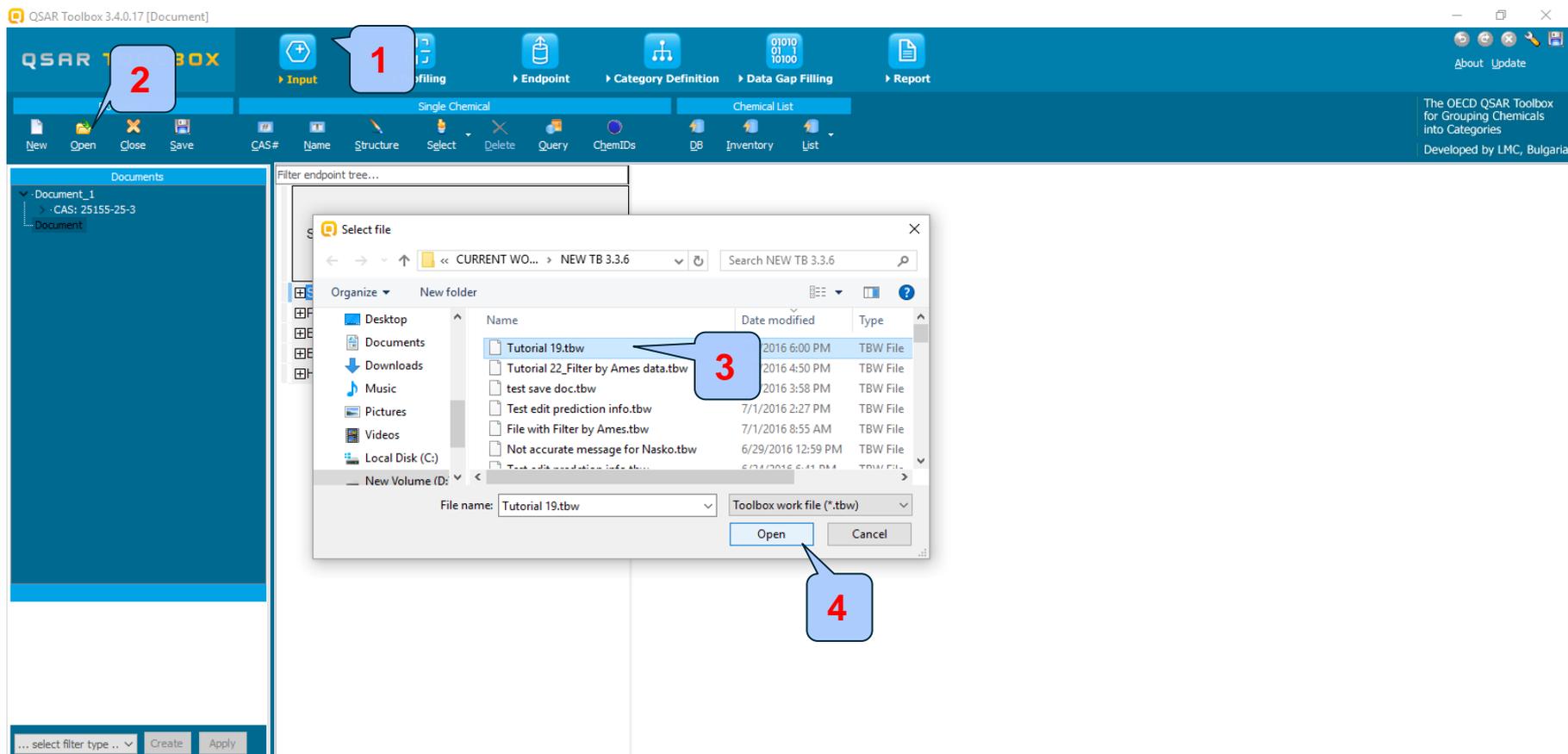
Outlook

- Background
- The exercise
- Workflow
 - Chemical Input
 - Profiling
 - Endpoint
 - Category definition
 - Data Gap Filling
 - Report
- **Save predictions**

Saving the prediction result

- This functionality allow storing/restoring the current state of Toolbox documents including loaded chemicals, experimental data, profiles, predictions etc, on the same computer. The functionality is implemented based on saving the sequence of actions that led to the current state of the Toolbox document and later executing these actions in the same sequence in order to get the same result(s).
- Saving/Loading the file with TB prediction is shown on next screenshots

Open saved file



Once the file has been saved **1. Go to Input; 2. Click Open; 3. Find and select file; 4. Click Open**