QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

OECD QSAR Toolbox v.3.0

Step-by-step example of how to predict Ames mutagenicity for a chemical by a qualitative read-across approach

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Outlook

- **Background**
- Objectives
- Specific Aims
- Read-across
- The exercise
- Workflow of the exercise

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Background

- This is a step-by-step presentation designed to take you through the workflow of the Toolbox in a data-gap filling exercise using read-across based on molecular similarity with data pruning.
- If you are a novice user of the Toolbox you may wish to review the "Getting Started" document available at [www.oecd.org/env/existingchemicals/qsar] as well as go through tutorials 1 and 2.

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Objectives

- **This presentation demonstrates a number of functionalities of the Toolbox:**
  - Entering a target chemical by SMILES notation and Profiling
  - Identifying analogues for a target chemical by molecular similarity
  - Retrieving experimental results available for those analogues, and for multiple endpoints
  - Filling data gaps by read-across

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Specific Aims

- To review the workflow of the Toolbox.
- To reacquaint the user with the six modules of the Toolbox.
- To reacquaint the user with the basic functionalities within each module.
- To introduce the user to new functionalities of selected modules.
- To explain to the rationale behind each step of the exercise.

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Read-across & the Analogue Approach

- Remember, read-across is a method that can be used to estimate missing data from a single or limited number of chemicals using the analogue approach.
- In the analogue approach, experimental 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" (i.e., within the same category).

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Analogous Chemicals

- Previously you learned that analogous sets of chemicals are often selected based on the hypothesis that the toxicological effects of each member of the set will show a common behaviour.
- For this reason mechanistic profilers and grouping methods have been shown to be of great value in using the Toolbox.
- However, there are cases where the mechanistic profilers and grouping methods are inadequate and one is forced to rely on molecular similarity to form a category.
- The Toolbox allows one to develop a category by using either a mechanistic category like DNA binding or structural similarity.
- Since there is no preferred way of identifying structural similarity, the user is guided to use DNA binding as a first option.

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Exercise

- In this exercise we will predict the Ames mutagenicity potential for an untested compound, (n-hexanal) [SMILES CCCCCC=O)], which is 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 structural similarity, in particular "DNA binding by OECD".
- The prediction itself will be made by "read-across" analysis.

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Side-Bar On Mutagenesis

- Mutagens do not create mutations.
- Mutagens create DNA damage.
- Mutations are changes in nucleotide sequence.
- Mutagenesis is a cellular process requiring enzymes and/or DNA replication, thus cells create mutations.

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Side-Bar On Mutagenesis

- Mutations within a gene are generally base-substitutions or small deletions/insertions (i.e., frameshifts).
- Such alteration are generally called point mutations.
- The Ames scheme based on strains of *Salmonella* provide the corresponding experimental data.

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Side-Bar On Mutagenesis

- The Ames mutagenicity assay (see OECD guideline 471) is designed to assess the ability of a chemical to cause point mutations in the DNA of the bacterium *Salmonella typhimurium*.
- The Ames test includes a number of strains (TA1537, TA1535, TA100, TA98 and TA97) that have been engineered to detect differing classes of mutagenic chemicals.
- The basic test only detects direct acting mutagens (i.e., those chemicals able to interact with DNA without the need for metabolic activation).

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Side-Bar on Metabolic Activation

- The inclusion of an S9 mix of rodent liver enzymes is designed to assess those chemicals requiring metabolic activation in order to be mutagenic.
- Typically, chemicals are assayed both without S9 and with S9 with results being reported in a binary fashion
- A positive result in any of the bacterial strains with or without S9 confirms mutagenic potential.

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- **Workflow of the exercise**

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Workflow

- **The Toolbox has six modules which are used in a sequential workflow:**
  - Chemical Input
  - Profiling
  - Endpoints
  - Category Definition
  - Filling Data Gaps
  - Report

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Outlook

- Background
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- Specific Aims
- Read-across
- The exercise
- **Workflow of the exercise**
  - **Chemical input**

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Chemical Input
Overview

- As you leader in the previous tutorials, 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 chemcial is the correct one.

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Chemical Input
Ways of Entering a Chemical

- **Remember there are several ways to enter a target chemical and the most often used are:**
  - CAS#,
  - SMILES (simplified molecular information line entry system) notation, and
  - Drawing the structure
- Click on **Structure**.
- This inserts the window entitled "2D editor" (see next screen shot).

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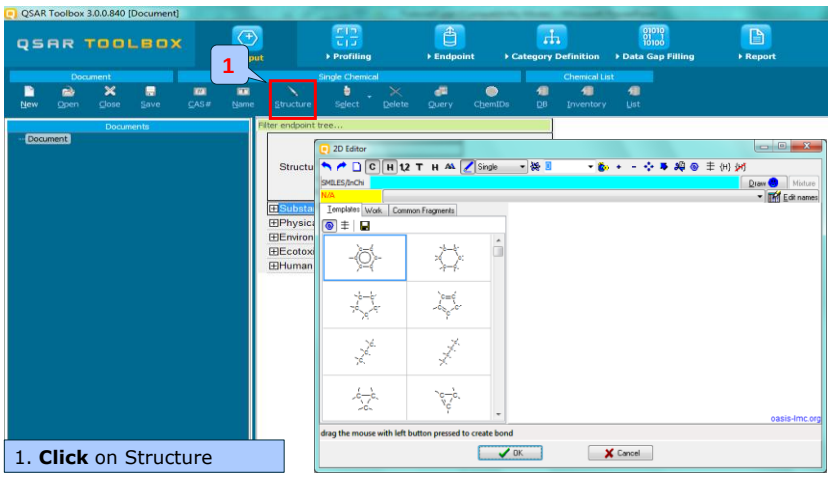
Chemical Input
Input target chemical by drawing



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Chemical Input
Input target chemical by SMILES

- In the Aqua-colored area next to "SMILES/InChi" type CCCCCC=O.
- Note as you type the SMILES code the structure is being drawn in the centre of the structure field (see next screen shot).
- Click "OK" to accept the target chemical.

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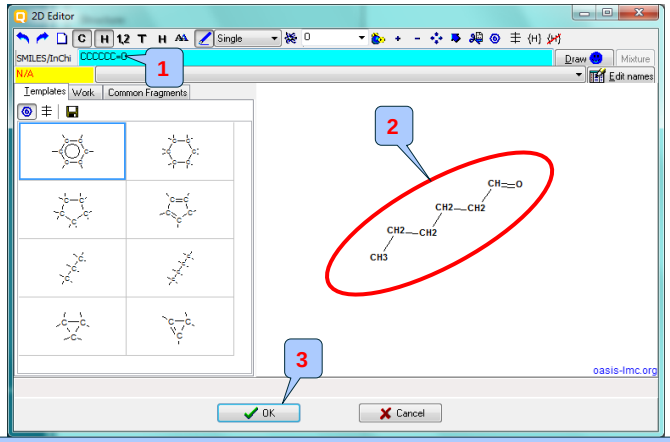
Chemical Input
Input target chemical by SMILES



1. **Type** CCCCCC=O in SMILES/InChi window; 2. 2D structure; 3. **Click** OK

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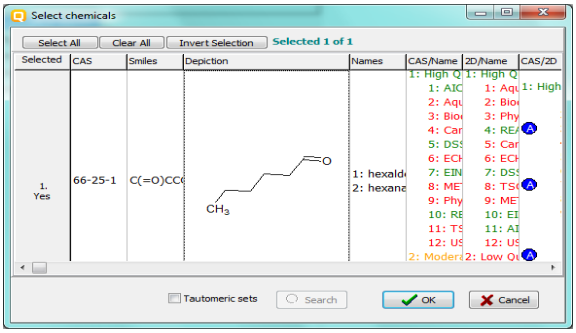
Chemical Input
Target chemical identity

The Toolbox now searches the Toolbox databases and inventories for the presence of the chemical with structure related to the current SMILES notation. It is depicted as a 2D image.



This panel displays QA information for presented chemicals. Click OK to add chemical in data matrix

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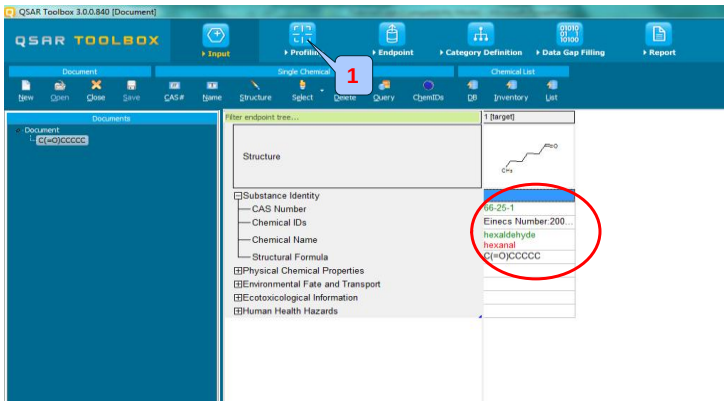
Chemical Input
Target chemical identity

- You have now selected your target chemical.
- Click on the box next to "Substance Identity"; this displays the chemical identification information (see next screen shot).
- It is important to remember that the workflow is based on the structure coded in SMILES.

Chemical Input
Target chemical identity



The workflow on the first module is now complete; click on "Profiling" [1] to move to the next module.

Outlook

- Background
- Objectives
- Specific Aims
- Read-across
- The exercise
- **Workflow of the exercise**
  - Chemical input
  - **Profiling**

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Profiling
Overview

- As you may remember, "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.
- Available profilers includes likely mechanism(s) of action which have been show to be useful in forming categories that include the target chemical.

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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 this example, the following general mechanistic profiling methods are relevant to genetic toxicity:
  - Protein binding by OASIS – mechanistic grouping
  - Protein binding by OECD – mechanistic grouping
  - DNA binding by OASIS v1.1– mechanistic grouping
  - DNA binding by OECD – mechanistic grouping
  - DNA alerts for AMES, MN and CA by OASIS v.1.1
  - Carcinogenicity (genotox and nongenotox) alerts by ISS
  - in vitro mutagenicity (Ames test) alerts by ISS
  - in vivo mutagenicity (Micronucleus) alerts by ISS
  - Organic function groups

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Profiling
Profiling the target chemical

- Select the "Profiling methods" related to the target endpoint.
- This selects (a green check mark appears) or deselects(green check disappears) profilers.
- For this example, select the profilers relevant to genetic toxicity (see next screen shot).

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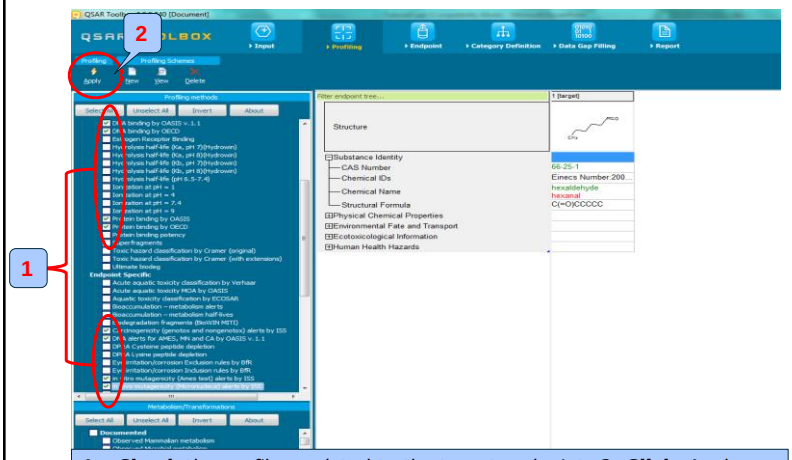
Profiling
Profiling the target chemical



1. Check the profilers related to the target endpoint; 2. **Click** Apply

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Profiling
Profiling the target chemical

- The actual profiling will take several seconds depending on the number and type of selected profilers.
- The results of profiling automatically appear as a dropdown box under the target chemical (see next slide).
- Please note the specific profiling results by DNA, Protein binding, and Organic functional groups.
- These results will be used to search for suitable analogues in the next steps of the exercise.

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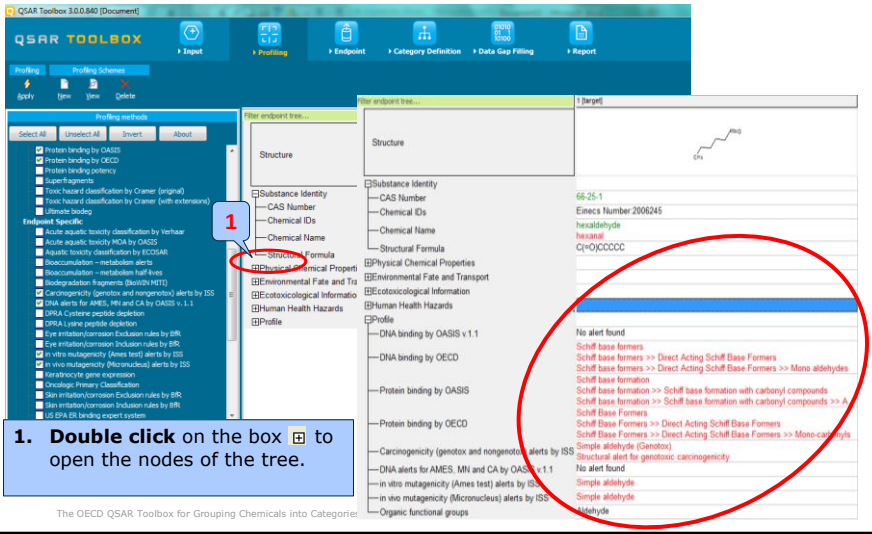
Profiling
Profiles of n-hexanal



1. **Double click** on the box ⊞ to open the nodes of the tree.

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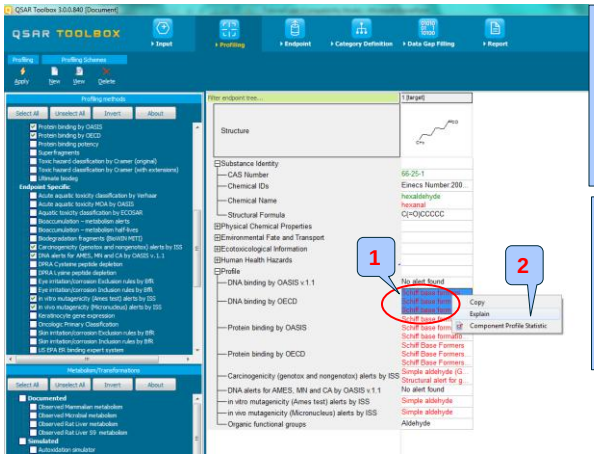
Profiling
Profiles of n-hexanal



- In this case there is structural evidence that it is a DNA and Protein binding compound.
- This allows to bind covalently to DNA .
- This mechanistic information is important for the grouping of analogues.

1. Right click on the box with profiling result by DNA binding by OASIS.
2. Left Click on the "Explain" box to see why the target is profiled as "Mono-aldehydes" by DNA binding by OECD (see next slide).

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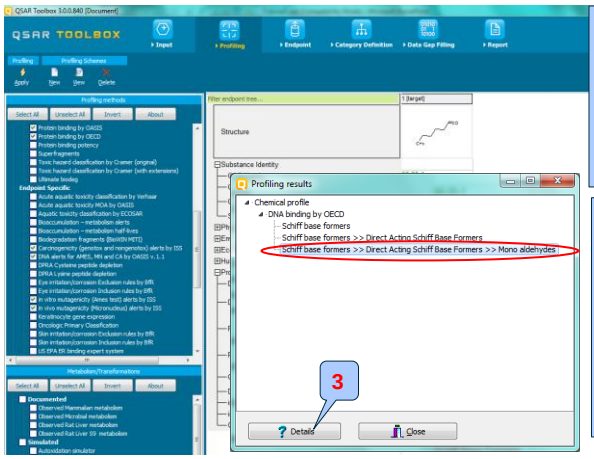
Profiling
Profiles of n-hexanal



- In this case there is structural evidence that it is a DNA and Protein binding compound.
- This allows to bind covalently to DNA .
- This mechanistic information is important for the grouping of analogues.

1. Right click on the box with profiling result by DNA binding by OASIS.
2. Left Click on the "Explain" box to see why the target is profiled as "Mono-aldehydes" by DNA binding by OECD (see next slide).
3. The window with chemical profiles appears, click "Details" to see detailed explanation

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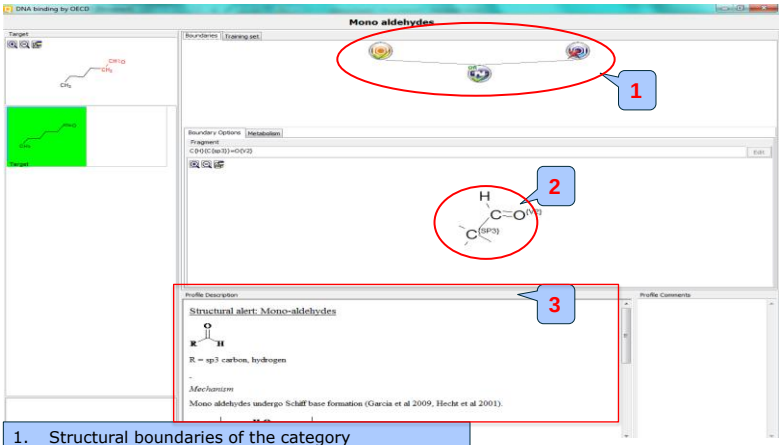
Profiling
DNA binding by OECD of n-hexanal



1. Structural boundaries of the category
2. Definition of the used common fragments
3. Mechanistic justification of the category

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- **Workflow of the exercise**
  - Chemical input
  - Profiling
  - **Endpoint**

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Endpoints
Overview

- As you should remember, "Endpoints" refer to the electronic process of retrieving the fate and toxicity data that are stored in the Toolbox database.
- Note, data can be gathered in a global fashion (i.e., collecting all data of all endpoints) or on more narrowly defined settings (e.g., collecting data for a single or limited number of endpoints).

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Endpoints
Case study

- In this example, we limit our data gathering to the common genotoxicity endpoints from databases containing toxicity data (Carcinogenicity & Mutagenicity ISSCAN , Micronucleus ISSMIC, Micronucleus OASIS, Genotoxicity OASIS and Toxicity Japan MHLW).

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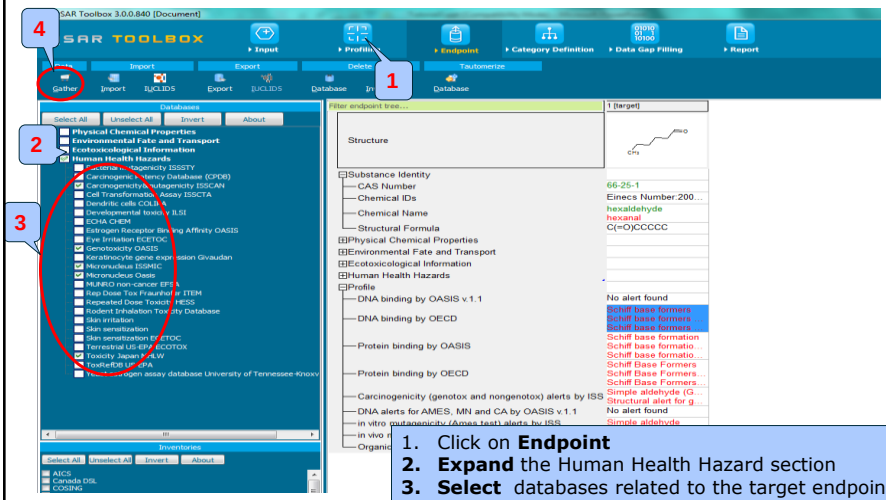
Endpoints
Gather data



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

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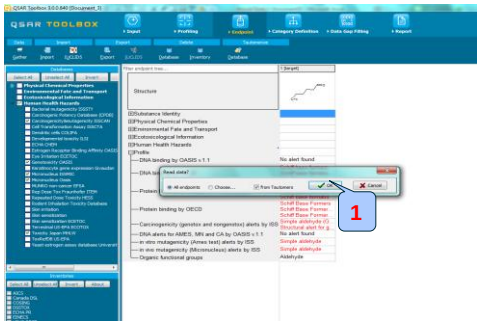
Endpoints
Process of collecting data

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.



1. **Click** OK to read all available data

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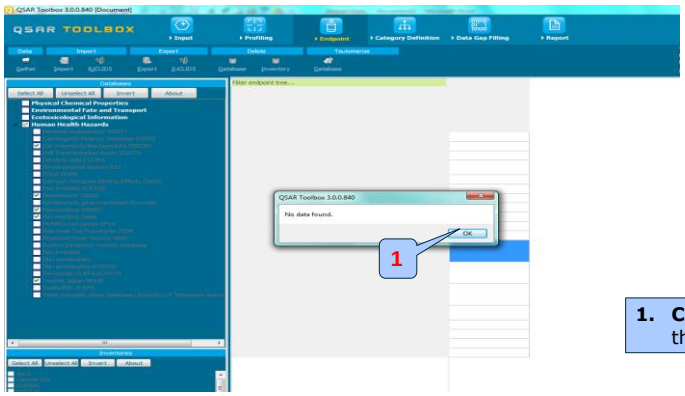
Endpoints
Process of collecting data

In this example, an insert window appears stating there was "no data found" for the target chemical.



1. **Click** OK to close the window

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Endpoints
Recap

- You have entered the target chemical by SMILES and found it to be n-hexanal with the CAS# [66-25-1].
- You have profiled the target chemical and found no experimental data is currently available for n-hexanal .
- In other words, you have identified a data gap, which you would like to fill in.
- Click on "Category definition" to move to the next module.

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  - Chemical input
  - Profiling
  - Endpoint
  - **Category definition**

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Category Definition
Overview

- As stated in the previous tutorials, this module provides the user with several means of grouping chemicals into a toxicologically meaningful category that includes the target molecule.
- Remember, this is the critical step in the workflow of the Toolbox.
- Several options are available in the Toolbox to assist the user in defining the category definition.

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Category Definition
Side-Bar on Mutagens

- It is important to remember that mutagens are really cell-damaging agents, which can create a wide array of adverse effects beyond damage to DNA.
- Lets take a moment to review our mechanistic profile of the target chemical (see next screen shots).

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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 downloaded from:
  http://www.oecd.org/dataoecd/58/56/46210452.pdf
- For this example, we will start from a specific DNA binding mechanism identified for the target chemical and find analogues which can bind by the same mechanism and for which experimental results are available.

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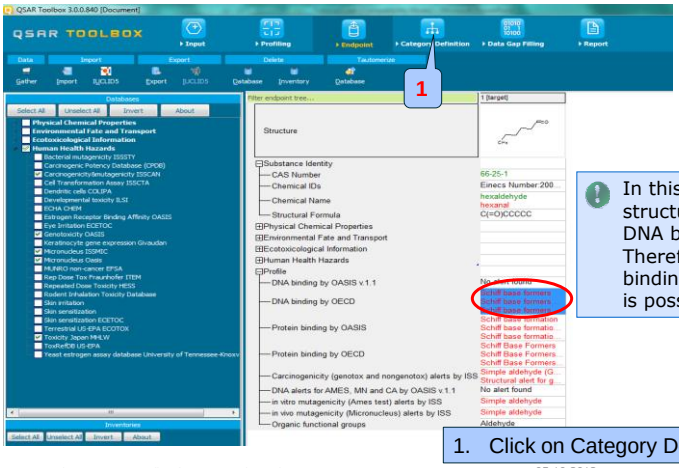
Category Definition
Which of the category to be defined?



In this case n-hexanal has structural evidence that it is a DNA binding compound. Therefore, grouping by DNA binding by OECD mechanism is possible.

1. Click on Category Definition

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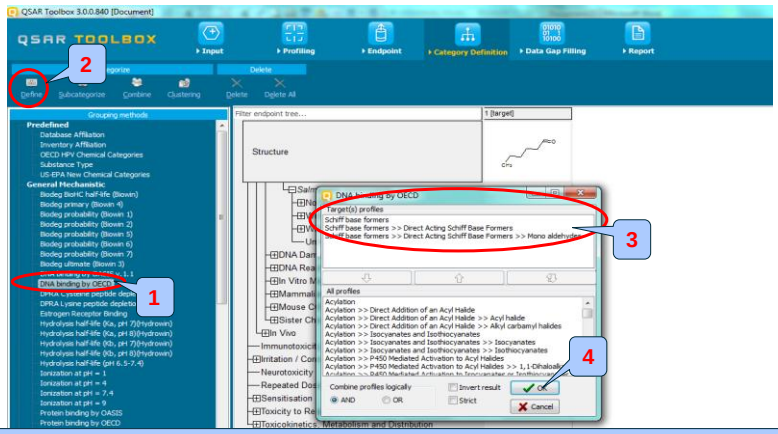
Category Definition
Defining DNA binding by OECD category



1. **Highlight** "DNA binding by OECD"; 2. **Click** Define; 3. The target category is Mono-aldehydes belonging to Direct acting Schiff base formers and Schiff base domain, Confirm the category; 4. **Click** OK

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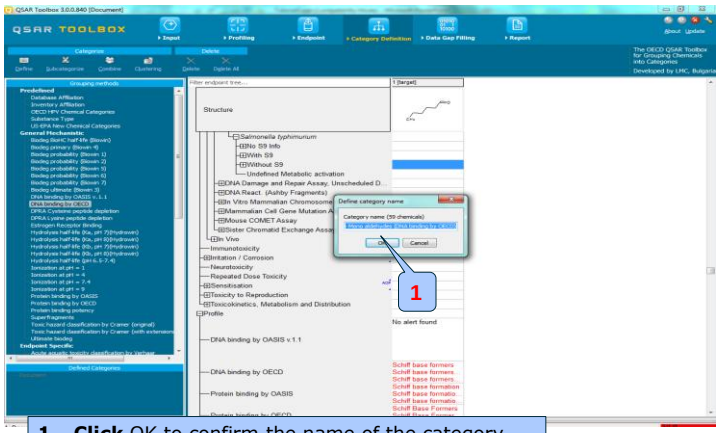
Category Definition
Defining DNA binding by OECD category



1. **Click** OK to confirm the name of the category

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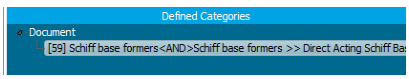
Category Definition
Analogues

- The Toolbox now identifies all chemicals corresponding to "Mono-aldehydes" by DNA binding by OECD listed in the databases selected under "Endpoints".
- The name of the category appear in the "Defined Categories" window, the number in brackets is the number of substances belonging to the category (59 analogues including the target chemical are identified)



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Category Definition
Read data for Analogues

- The Toolbox automatically request the user to select the endpoint that should be retrieved
- The user can either select the specific endpoint or by default choose to retrieve data on all endpoints (see below)

- **In this example, as only databases are selected that contain information for genetic toxicity endpoint, so both options give the same results.**

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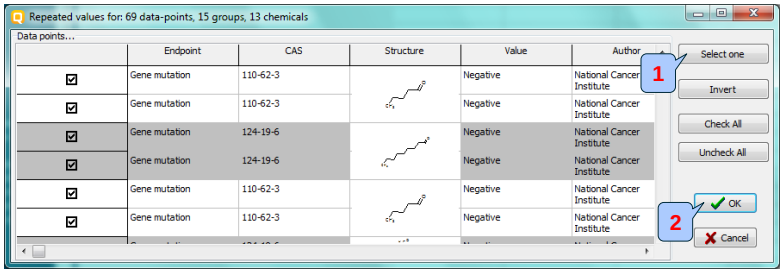
Category Definition
Read data for Analogues

Due to the overlap between the Toolbox databases same data for intersecting chemicals could be found simultaneously in more than one databases. The data redundancy is identified and the user has the opportunity to select either a single data value or all data values.



1. **Click** Select one and then 2. **Click** OK

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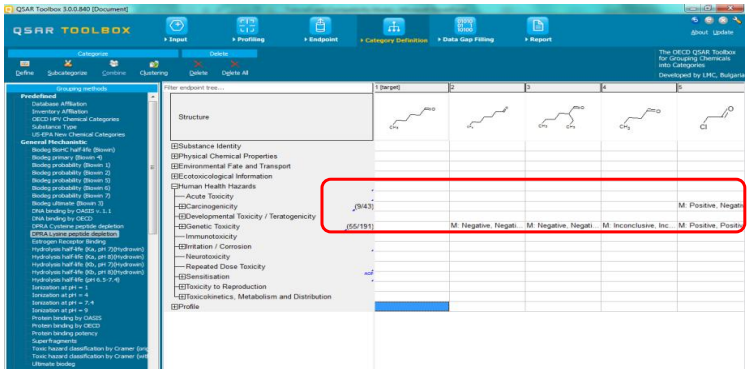
Category Definition
Summary information for Analogues

The experimental results for the analogues are inserted into the matrix.



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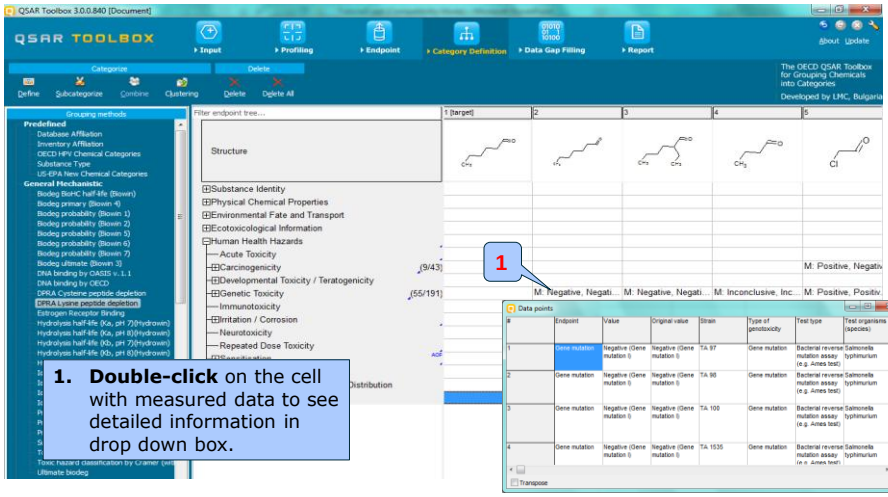
Category Definition
Side-Bar of experimental data



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Category Definition
Recap

- You have identified a mechanistic category consisting of 59 analogous ("Mono-Aldehydes" by DNA binding by OECD classification) with the target chemical (n-hexanal).
- The available experimental data for these 59 similar chemicals are collected from the previously selected databases under Endpoint section.
- The user can proceed with "Filling data gap" module, but before that he/she should navigate throw the endpoint tree and find the gap that will be filled in.

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Category Definition
Navigation throw the endpoint tree

- The user can navigate through the data tree by closing or opening the nodes of the tree.
- In this example, results from genotox testing are available (see next screen shot).
- In this example to see does the target is mutagenic or not, it is recommended to check subsequently the two mutagenic endpoints:
  - Ames without S9
  - Ames with S9
- By double clicking on the nodes of endpoint tree open the tree to the target :**Bacterial reverse mutation (Ames) assay without S9** *(i.e., double click on Human Health Hazards then double click on Genetic Toxicity followed by In Vitro and Bacterial Reverse Mutation Assay (e.g. Ames Test),Gene Mutation Salmonella typhimurium, Without S9)* (see next screen shot).

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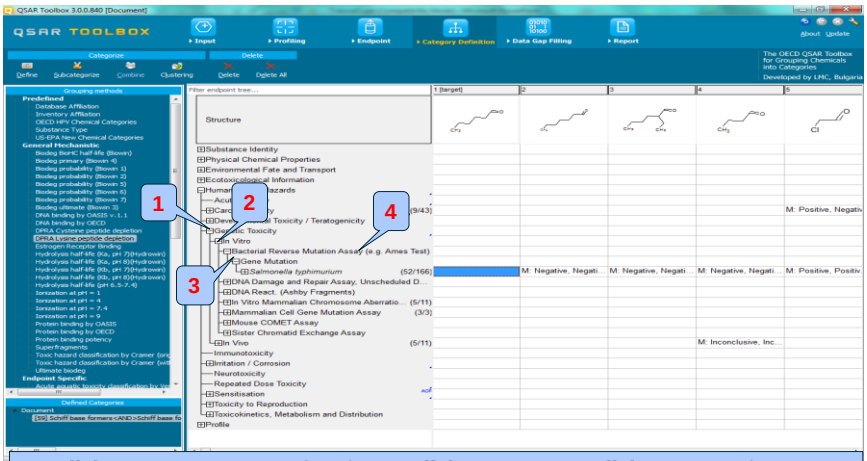
Category Definition
Navigation throw the endpoint tree



1. **Click** to Genetic Toxicity after that 2. **Click** to In vitro 3. **Click** to Bacterial Reverse Mutation Assay (e.g. Ames Test) and finally **3. Click** Gene Mutation

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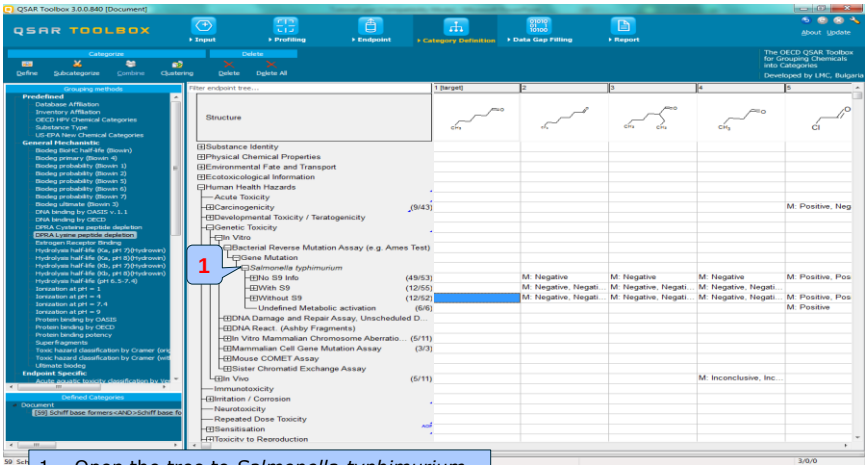
Category Definition
Navigation throw the endpoint tree



1. Open the tree to *Salmonella typhimurium*

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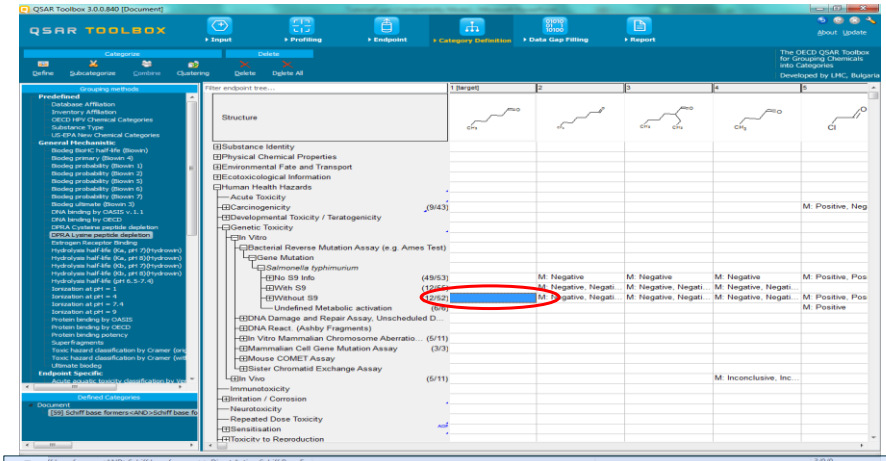
Category Definition
Navigation throw the endpoint tree



In order to examine the target endpoint "Ames without S9", select the cell as shown.

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Category Definition
Recap

- You have now retrieved the available experimental data on genetic toxicity for 59 chemicals classified as "Mono-aldehydes" by DNA binding by OECD, found in the databases containing mutagenicity data.
- Out of 59 only 12 have experimental mutagenicity data related to the target.
- You are now ready to fill in the data gap.
- In this example with qualitative mutagenicity data we can only use read-across.

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Outlook

- Background
- Objectives
- Specific Aims
- Read-across
- The exercise
- **Workflow of the exercise**
  - Chemical input
  - Profiling
  - Endpoint
  - Category definition
  - **Data Gap Filling**
    - **Ames without S9**

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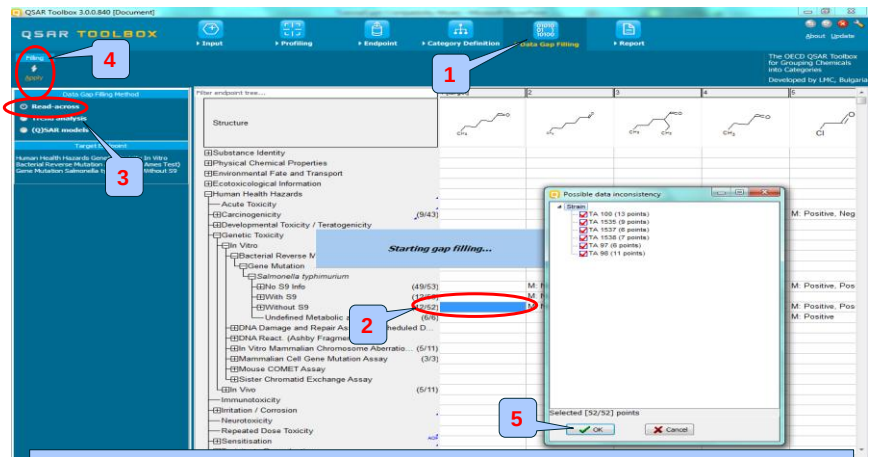
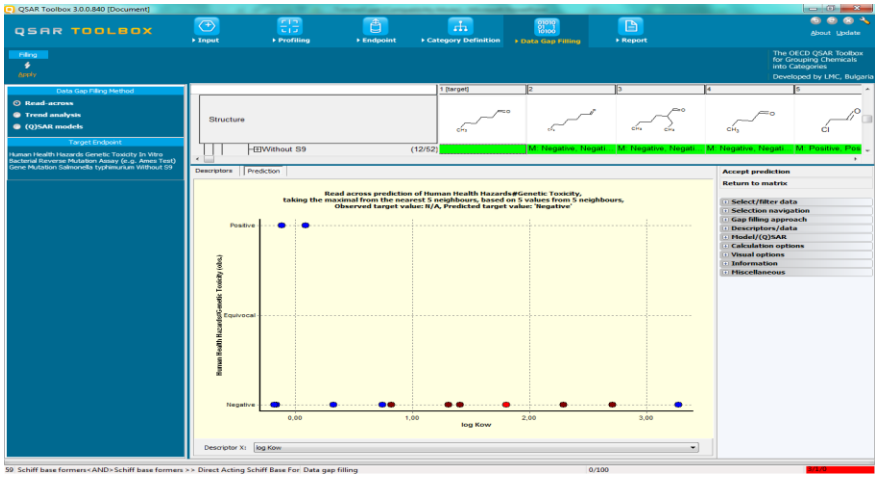
Data Gap Filling(Ames without S9)
Apply read-across



1. Click on Data Gap Filling; 2. **Highlight** the data endpoint box corresponding to Ames without S9 under the target chemical (note it is empty); 3. **Select** Read across and; 4.**Click** Apply; 5. An insert window alerting you to possible data inconsistencies appears. **Click** OK.

QSAR TOOLBOX

Data Gap Filling(Ames without S9)
Results of Read across



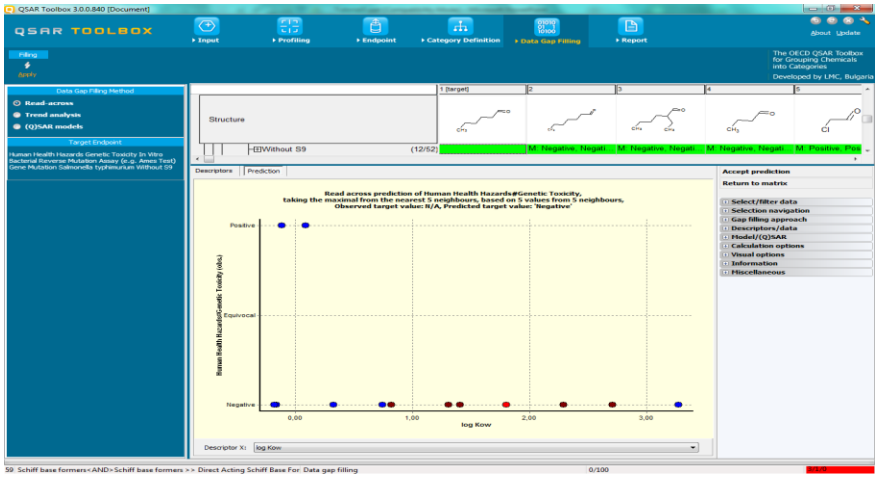
QSAR TOOLBOX

Data Gap Filling(Ames without S9)
Interpreting Read-across

- The resulting plot outlines the experimental Ames results of all analogues (Y axis) according to a descriptor (X axis). Note, Log Kow is on the X-axis; while this descriptor is not significant to Ames data, it is the default descriptor for data gap filing (see next screen shot).
- The **RED** dot represents the predicted value for target chemical (see next screen shot).
- The **PURPLE** dots represent the observed value for the target neighbours(analogues) used for read-across (see next screen shot).
- The **BLUE** dots represent the experimental results available for the analogues but not used for read-across. (see next screen shot).
- Please note **GREEN** dots (which you will see shortly) represent analogues belonging to different subcategories.

QSAR TOOLBOX

Data Gap Filling(Ames without S9)
Results of Read across



QSAR TOOLBOX

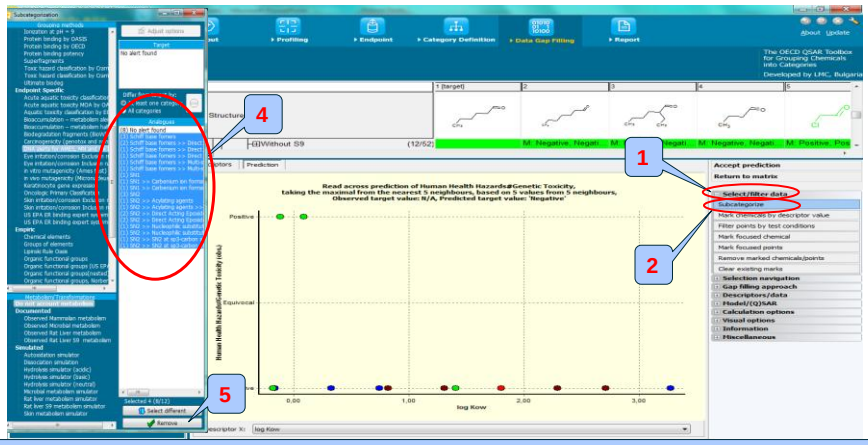
Data Gap Filling(Ames without S9)
Interpretation of the Read across

- Two of the analogues are mutagenic in the Ames assays without S9, the rest analogues are non-mutagenic
- Non-mutagenic potential (Negative) is, therefore, predicted with confidence for the target chemical.
- However, before data gap filling it is recommended to check the similarity of the analogues used in the prediction (see next screen shot). This is performed in order to assure the category consists of analogues that are both mechanistically and structurally similar.

QSAR TOOLBOX

Data Gap Filling(Ames without S9)

Subcategorization by DNA binding by OASIS

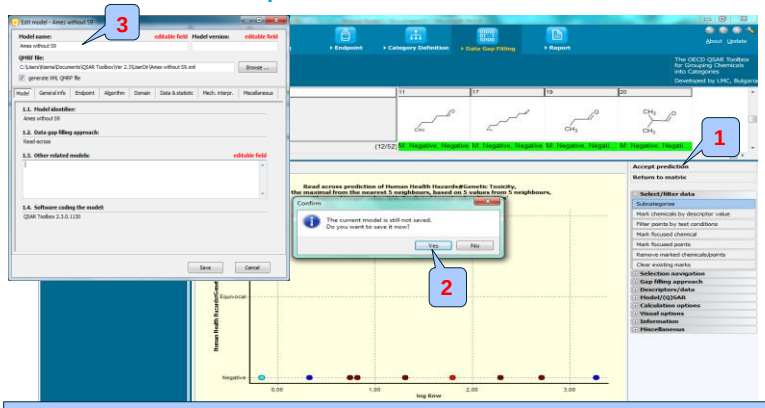


1. **Select** Select/filter data; 2. **Select** Subcategorize; 3. **Select** DNA alert for AMES, MN and CA by OASIS; 4. Examine dissimilar chemicals and 5. **Click** Remove to eliminate dissimilar chemical.

QSAR TOOLBOX

Data Gap Filling(Ames without S9)

Interpretation of the Read across

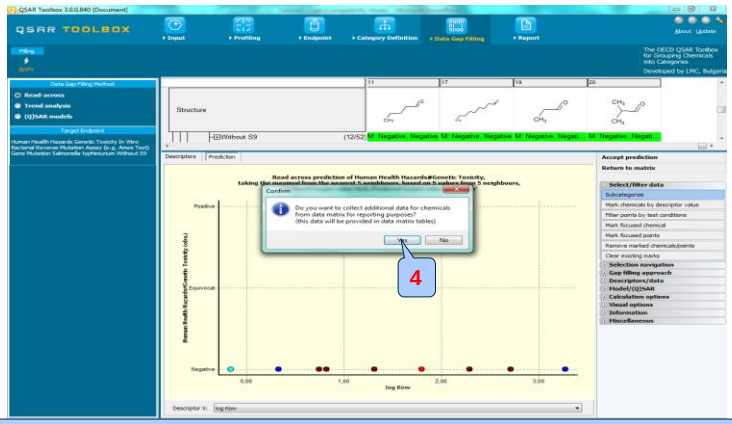


Now all analogues are structurally (Aldehydes) similar, then the prediction could be accepted by

1. **Click** on Accept prediction
   If you want to save the model, and use it for further predictions, then
2. **Click** Yes and then 3. **Edit** the information about the model.

QSAR TOOLBOX

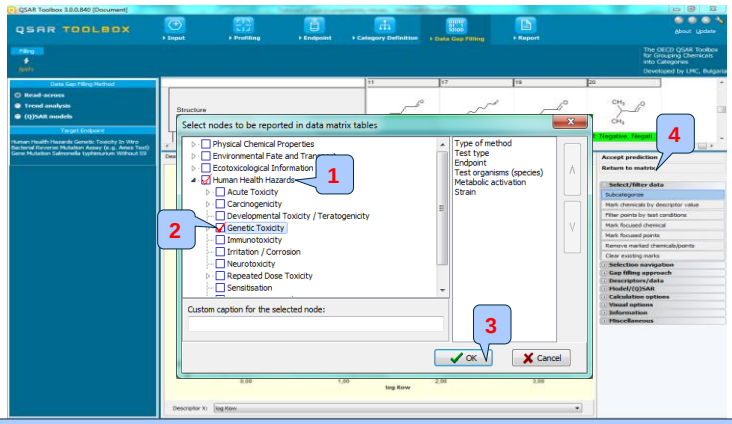
Data Gap Filling(Ames without S9)
Interpretation of the Read across



3. Click **Yes in order** to have in report additional data for the analogues

QSAR TOOLBOX

Data Gap Filling(Ames without S9)
Interpretation of the Read across



1. **Expand** the Human Health hazard section
2. **Select** Genetic toxicity
3. **Click** OK
4. Return to matrix

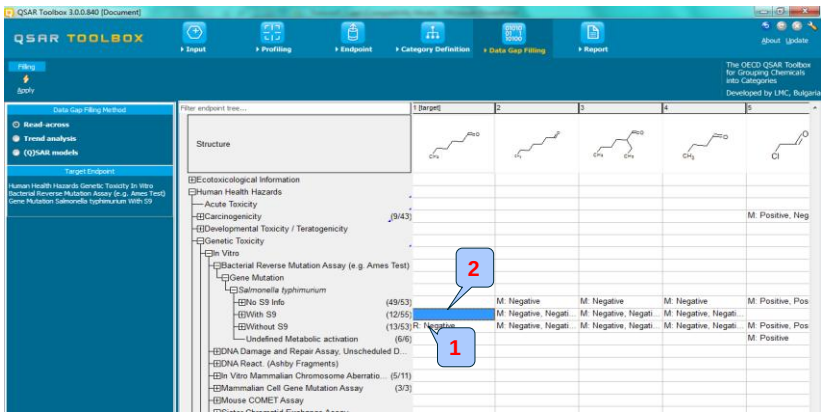
QSAR TOOLBOX

Data Gap Filling(Ames without S9)
Results

- By accepting the prediction the data gap is filled.
- By clicking on "Return to Matrix", the user can close the read-across for the current endpoint and proceed with the workflow for the second endpoint, which in this case will be "Ames with S9" (see next screen shot).

QSAR TOOLBOX

Data Gap Filling(Ames without S9)
Results



1. This is the prediction for the first endpoint.
2. This is the data gap for the second endpoint.

QSAR TOOLBOX

Outlook

- Background
- Objectives
- Specific Aims
- Read-across
- The exercise
- **Workflow of the exercise**
  - Chemical input
  - Profiling
  - Endpoint
  - Category definition
  - **Data Gap Filling**
    - Ames without S9
    - **Ames with S9**

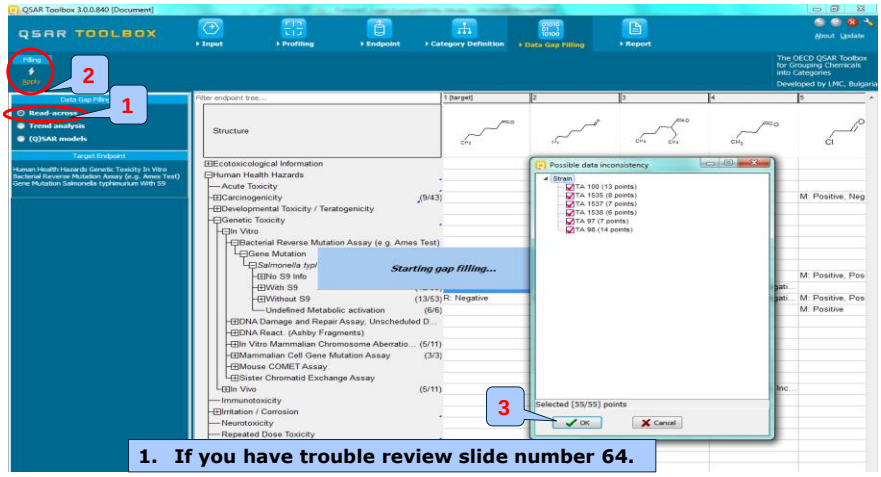
QSAR TOOLBOX

Data Gap Filling(Ames with S9)

- We do this the same way as with Ames without S9.
- Make sure **Data Gap Filling** is highlighted.
- Highlight the **data endpoint box**; this time corresponding to **Ames with S9**. Again the box under the it is empty.
- Select **Read across** and Click **Apply.**
- As before an insert window alerting you to **possible data inconsistencies** appears. Click **OK** (see next screen shot).

QSAR TOOLBOX

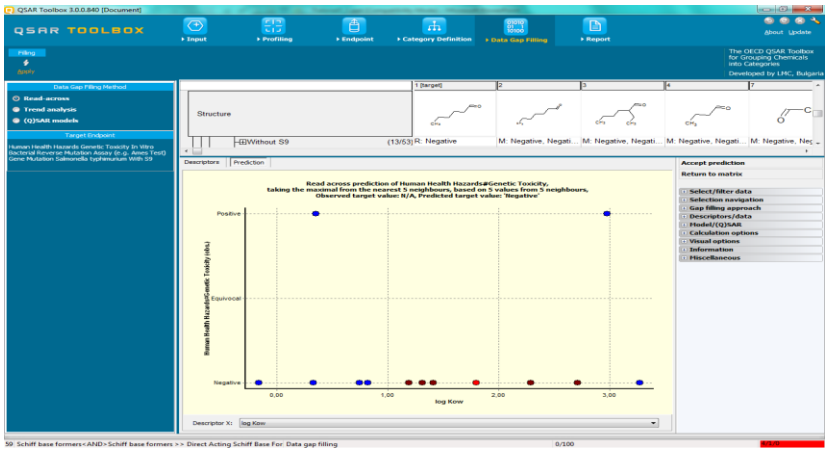
Data Gap Filling(Ames with S9)
Apply read-across



1. **If you have trouble review slide number 64.**

QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Results of Read across



QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Results of Read across

- As with Ames without S9, before accepting the estimated result for the target chemical, by read-across the user should refined the category by subcategorisation.
- Subcategorisation refers to the process of applying additional profilers to the previously defined category, identifying chemicals which have differing profiling results and eventually eliminating these chemicals from the category.
- In this example, we are going to use several different profilers to repeatedly subcategorise the data set.

QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Side Bar of Subcategorization

The analogues which are dissimilar to the target chemical with respect to:

- Organic functional groups – The categorization based on this profiler identifies analogues having the same organic functional groups.
- Structural similarity – The categorization based on this identifies the most structurally similar chemicals (In this case refine analogues below 50%).

can be removed from the initial list of analogues previously defined by DNA binding by OECD.

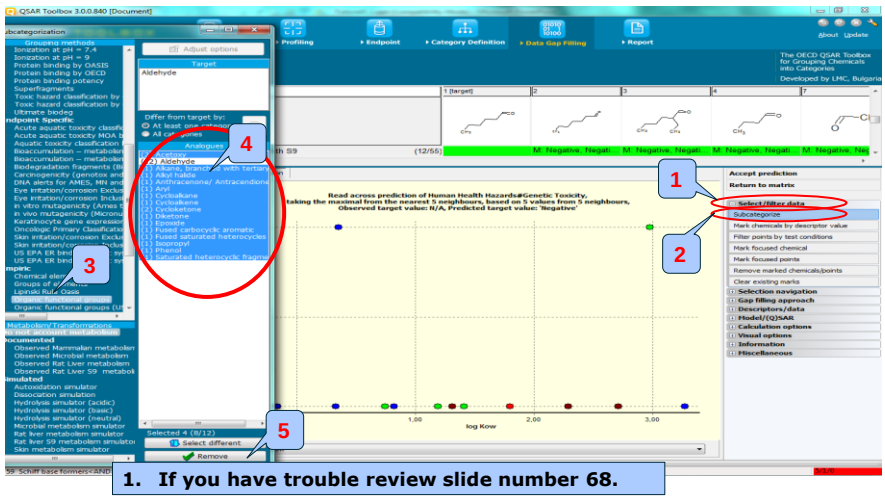
QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Subcategorization by Organic functional groups

- As with Ames without S9, we want to refined the category by subcategorisation with DNA binding by OASIS.
- Select **Select/filter data**
- Select **Subcategorize**
- Select **Organic functional groups**
- Look for dissimilar chemicals
- Click **Remove** to eliminate dissimilar chemical.

QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Subcategorization by Organic functional groups



1. **If you have trouble review slide number 68.**

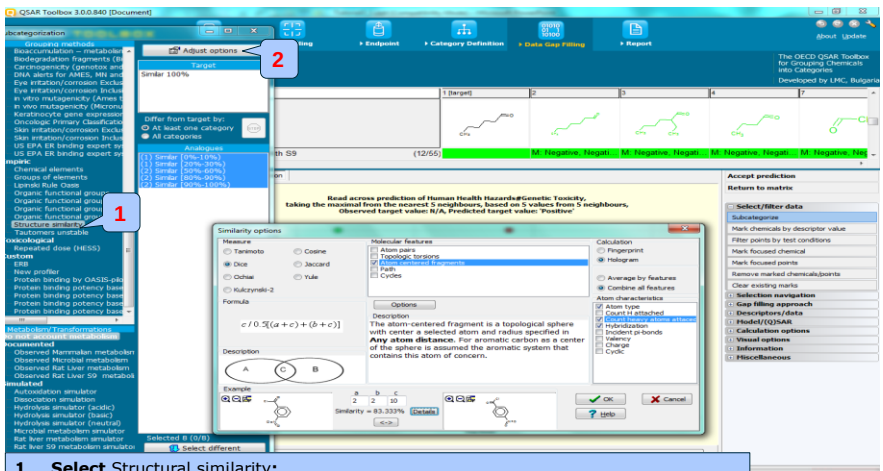
QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Subcategorization by structural similarity

- While it is the method of last resort Toolbox provides the user with the option for subcategorizing by structural similarity.
- This is done by using the "Structural similarity" profiler and then setting the percent similarity desired (see next screen shot).

QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Subcategorization by structural similarity



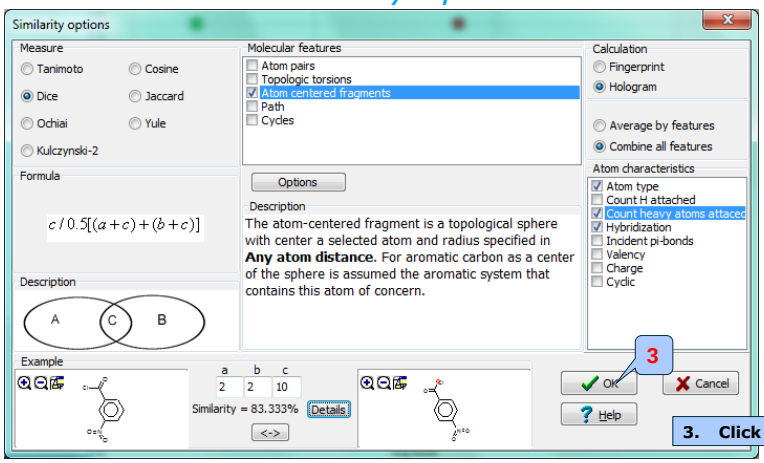
1. **Select** Structural similarity;
2. **Adjust** the options of similarity as shown in the next slide

QSAR TOOLBOX

Data Gap Filling(Ames with S9)

Subcategorization by structural similarity

Similarity options

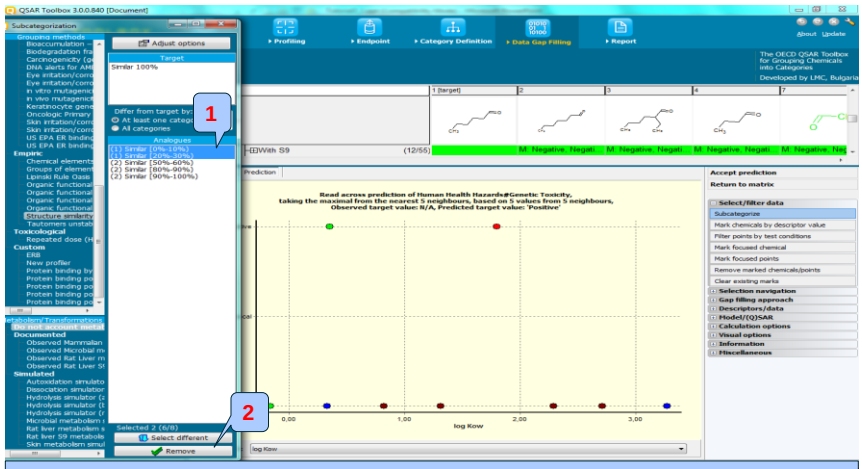


3. Click OK

QSAR TOOLBOX

Data Gap Filling(Ames with S9)

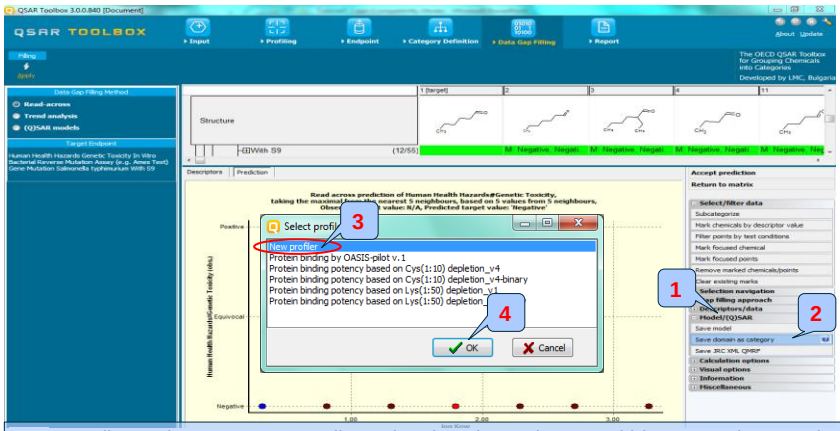
Subcategorization by structural similarity



1. **Select the** analogues with less than 50% similarity by highlighting the lower % groups;
2. **Click** Remove to eliminate dissimilar chemicals (i,e., the ones marked in green).

QSAR TOOLBOX

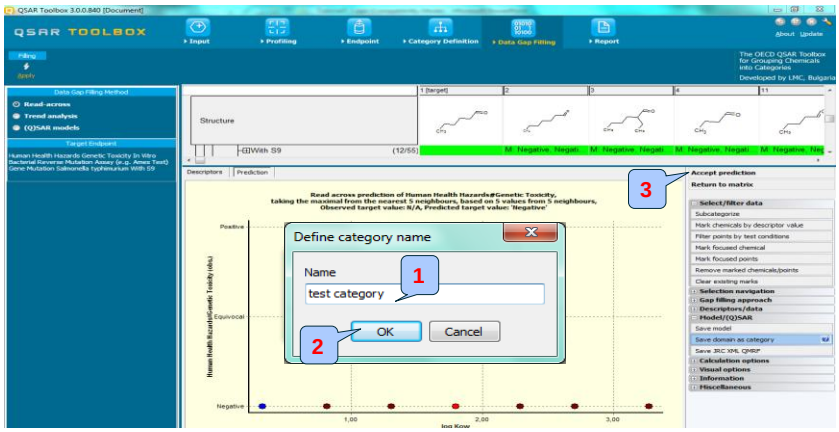
Data Gap Filling(Ames with S9)
Result of read-across



Now all 5 analogues are structurally similar, then the prediction could be accepted or saved as a category(domain) in the profiler by
1. **Click** on Model/(Q)SAR and then; 2. **Click** on Save domain as category
3. Since a custom profiler has previously been defined, **highlight** custom profiler and 4. **Click** OK.

QSAR TOOLBOX

Data Gap Filling(Ames with S9)
Result of read-across



1. **Type** a name for the category in the "Name" box; 2. **Click** OK; 3. **Click** Accept prediction and Return to matrix.

QSAR TOOLBOX

Outlook

- Background
- Objectives
- Specific Aims
- Read-across
- The exercise
- **Workflow of the exercise**
  - Chemical input
  - Profiling
  - Endpoint
  - Category definition
  - Data Gap Filling
  - **Report**

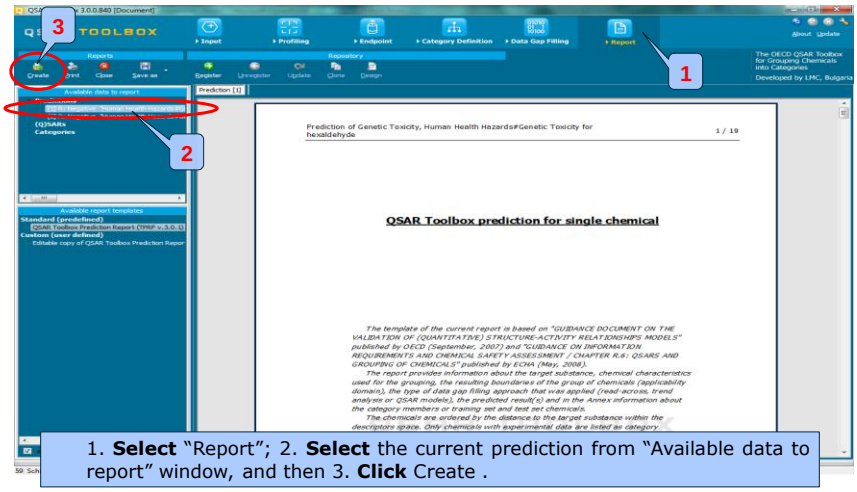
QSAR TOOLBOX

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 define their own user defined templates.
- The report can then be printed or saved in different formats. (see next screen shot).

QSAR TOOLBOX

Report
Generate Report



1. **Select** "Report"; 2. **Select** the current prediction from "Available data to report" window, and then 3. **Click** Create .

QSAR TOOLBOX

Congratulation

- By now you should feel comfortable with the six basic modules of the toolbox and how they form the work flow of the Toolbox.
- In this tutorial you have now been introduced to several additional function in the Toolbox, especially using different profilers in subcategorizing the category of the target chemical.
- Remember proficiency in using the Toolbox will only come with practice.