OECD (Q)SAR Toolbox v.4.4

Tutorial on using the PBT prioritization scheme
Outlook

• **Aim**
• Keywords
• PBT scheme
• Workflow of the prediction
• Export of the results
Aim

This is a step-by-step presentation designed to take the user of Toolbox through the PBT prioritization scheme implemented in the software.
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Keywords

TARGET CHEMICAL - chemical of interest

MODULE – a Toolbox module is a section dedicated to specific actions and options (e.g. Profiling)

WORKFLOW – the use, in combination, of the different modules (e.g. prediction workflow: from input to report)

PROFILER - algorithm (rule set) for the identification of specific features of the chemicals. Several types of profilers are available, such as structural (e.g. Organic functional groups), mechanistic (e.g. Protein binding by OECD) and endpoint-specific (e.g. in vitro in vitro mutagenicity (Ames test) alerts by ISS) profilers.

ALERT - the profilers consist of sets of rules or alerts. Each of the rules consists of a set of queries. The queries could be related to the chemical structure, physicochemical properties, experimental data, comparison with the target or list with substances and external queries from other predefined profilers (reference queries).

CATEGORY – “group” of substances sharing same characteristics (e.g. the same functional groups or mode of action). In a typical Toolbox workflow, it consists of the target chemical and its analogues gathered according to the selected profilers

ENDPOINT TREE – Endpoints are structured in a branched scheme, from a broader level (Phys-Chem properties, Environmental Fate and transport, Ecotoxicology, Human health hazard) to a more detailed one (e.g. EC3 in LLNA test under Human health hazard-Skin sensitization)

EXPORT – Toolbox allows to export data and predictions for chemicals in an Excel format

DATA MATRIX – Table reporting the chemical(s) and data (experimental results, profilers outcomes, predictions). Each chemical is in a different column and each data in a different row
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Background:

PBT prioritization scheme

• The PBT prioritization scheme is based on experimental data and (Q)SAR models.

• A substance is classified based on thresholds for persistence, bioaccumulation and toxicity, and the following classifications could be assigned:
  - very persistent (vP),
  - persistent (P),
  - very bioaccumulative (vB),
  - bioaccumulative (B),
  - very toxic (vT),
  - toxic (T).

• The thresholds are illustrated in the table on the next slide.
# Background:
## PBT assessment criteria

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
<th>Guidance</th>
<th>Data and models</th>
</tr>
</thead>
<tbody>
<tr>
<td>vP</td>
<td>$\text{BOD} \leq 30%$</td>
<td>REACH Annex XIII [1]</td>
<td>Experimental data only</td>
</tr>
<tr>
<td>P</td>
<td>$30% &lt; \text{BOD} \leq 40%$ or biodegradation probability $&lt; 0.5$</td>
<td>REACH Annex XIII [1]</td>
<td>Experimental data and BIOWIN 5 and 6 models</td>
</tr>
<tr>
<td>vB</td>
<td>$\text{BCF} \geq 3.699 \log(\text{L/kg wet})$</td>
<td>REACH Annex XIII [1]</td>
<td>Experimental data and BCFWIN model</td>
</tr>
<tr>
<td>B</td>
<td>$3.301 \leq \text{BCF} &lt; 3.699 \log(\text{L/kg wet})$ or $\log \text{Kow} &gt; 4.5$</td>
<td>REACH Annex XIII [1]</td>
<td>Experimental data and BCFWIN and KOWWIN models</td>
</tr>
<tr>
<td>vT</td>
<td>$\text{LC50} \leq 1 \text{ mg/l}$</td>
<td>GHS classification [2]</td>
<td>Experimental data only</td>
</tr>
<tr>
<td>T</td>
<td>$1 \text{ mg/l} &lt; \text{LC50} \leq 10 \text{ mg/l}$</td>
<td>GHS classification [2]</td>
<td>Experimental data only</td>
</tr>
</tbody>
</table>


Background: PBT assessment criteria

PBT priority grouping:

Based on the collected experimental data and results provided by (Q)SAR models, the system applies the worst case scenario to categorize chemicals using the following priority:

- With the **highest priority** are chemicals with available experimental data for P, B or T assessment.
- In case of unavailable experimental data for P, B or T, (Q)SAR models are applied for making predictions.

\[ \text{vP, vB or vT} \]
\[ \text{P, B or T} \]
\[ \text{notP, notB notT}. \]
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  ➢ Implementation

• Workflow of the prediction

• Export of the results
The PBT prioritization scheme is a graph of logically connected nodes.

The nodes are divided into three groups based on the P, B or T classification for hazard assessment.
Implementation of PBT prioritization scheme

- Each node (1) contains a data or parametric (model) boundary (2) where the criteria for PBT assessment are set.
- Data query is depicted here.
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• **Workflow of the prediction**

• Export of the results
Workflow of the prediction: Steps

- Input of target chemical(s)
- Profiling: Example prioritization scheme (PBT)
- Report
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• **Workflow of the prediction**
  ➢ Chemical input

• Export of the results
• 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

I. Single target chemical:
   • Chemical Name
   • Chemical Abstract Services (CAS) number (#)
   • SMILES (simplified molecular information line entry system) notation
   • Chemical with defined composition
   • Drawing chemical structure
   • Select from User List/Inventory/Databases

II. Group of chemicals:
   • User’s List
   • Inventory/Database
Chemical Input: Single chemical

• Open the Toolbox.
• Click on “Input” (see next screen shot).
1. Click **Input** (1) to display the main Input section (2).
1. Click **CAS#** (1);
2. Type in the **CAS #** 57-74-9 (the target chemical) (2); 
3. Click on **Search** (3);
4. Select the chemical (4);
5. Click **OK** (5).
Chemical Input
Single chemical: CAS RN

The chemical is displayed in the data matrix (1).
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• **Workflow of the prediction**
  ➢ Chemical input
  ➢ **Profiling**

• Export of the results
Profiling Overview

• “Profiling” refers to the electronic process of retrieving relevant information on a compound which is stored in the Toolbox, other than its fate and (eco)toxicity data.

• Toolbox has many predefined profilers but it also allows the user to develop new profilers.
1. Select **Profiling tab** (1);
2. Click **Unselect All** (2);
3. Tick **Example prioritization Scheme (PBT)** (3);
4. Click on **Apply** (4).
5. Expand the cell to see the results: P, vB, vT.
6. Double-click on the profiling results cell (5)
7. The results are explained in the next slides.
Profiling: explanation of “P” prediction

1. Left-click on the profiling results (1)
2. Click Explain in the pop-up window (2)
3. The Profiling results window is displayed (3)
4. Select “P” (4)
5. Click Details (5)
6. The PBT scheme is displayed and the query, which gives the prediction is shown (see next slide)
1. The “P” node (1), which criteria are fulfilled, is coloured in green and has a check mark. A yellow border around the node indicates that it is selected and its explanation is displayed in the Literature panel (2).

2. The nodes, which criteria are not fulfilled are colored in red and marked with “X” sign (3).

Biodeg probability = -0.267
1. Click **Definition** tab (1).
2. A red circle around the query indicates that it is selected (2).
3. Here it is a parametric query, which content is shown in the **Parameter query** tab (3).
4. Biodegradation probability (Biowin 5) model is incorporated in that query (4). The predicted outcome has to be below 0.5 (5) in order for the requirements to be fulfilled.

\[ \text{Biodeg probability} = -0.267 \]
Profiling: explanation of "vB" prediction

1. Left click on the profiling results cell (1).
2. Click **Explain** in the pop-up window (2).
3. The **Profiling results** window is displayed (3).
4. Select "vB" (4).
5. Click **Details** (5).
6. The PBT scheme is displayed and the query, which gives the prediction is shown (see next slide)
1. The node, which criteria are fulfilled is colored green and marked with "V" sign (1).
2. Here it is a node containing experimental data. The logic implemented in the PBT scheme implies that if the target chemical has experimental data (in this case vB) then the consecutive nodes from the bioaccumulation assessment are not run. Hence they are colored in grey (2).
3. All experimental data available for the target chemical is listed in the Explanation panel (3). The unit is L/kg.
Profiling: explanation of “vB” prediction

1. Expand the experimental result from the arrow next to the digits (1).
2. By moving the scroll bar (2), you can see all details of the measured data (3).
Profiling: explanation of "vT" prediction

1. Left click on profiling result cell (1).
2. Click Explain in the pop-up window (2).
3. The Profiling results window is displayed (3).
4. Select "vT" (4).
5. Click Details (5).
6. The PBT scheme is displayed and the query, which gives the prediction is shown (see next slide).
1. The node, which criteria are fulfilled is colored green and marked with “V” sign (1).

2. Here it is a node with experimental data. The logic implemented in the PBT scheme implies that if the target chemical has experimental data (in this case vT) then the consecutive nodes from the toxicity assessment are not run. Hence they are colored in grey (2).

3. All experimental data available for the target chemical is listed in the Explanation panel (3). The unit is mg/L or ppb. However only mg/L is considered (see slide 30).

4. The rules by which experimental data is collected were shown in the Literature tab (4).
1. Select **Definition** tab (1).
2. The details of the **Data query** (2), are shown in the Query details panel (3).
3. By moving the scrollbar, you can see the type of metadata included in the query.
4. In this example, the type of experimental data is **Any** (4) meaning that all available data is checked, but only data in mg/L and mean value ≤ 1 mg/L is considered.
1. Expand the experimental data from the arrow next to the digits (1)
2. By moving the scroll bar (2), you can see all details of the measured data
1. A **Viewfinder** (1) is displayed by clicking on the cross sign (2).
2. It contains navigation options for viewing the PBT scheme (3).
Profiling: common features of PBT interface

Properties, Literature and Scheme tabs gives more information about the query (properties), the node (literature) and the developer (scheme) (1).
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  ➢ Profiling

• Export of the results
Export of the results

1. Right click next to the name of the scheme (1)
2. Select **Export Data matrix** (2)
1. Expand structure info (1) and check **Chemical name(s)** (2).

2. **Example Prioritization Scheme (PBT)** is selected by default (3).

3. Click **Export** (4).
Export of the results

1. Type in the name of the file (1).
2. The files are only saved in .csv format (2).
3. Click Save (3).
4. Click OK in the confirmation message (4).
The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

Export of the results

<table>
<thead>
<tr>
<th></th>
<th>CAS Number</th>
<th>Chemical name(s)</th>
<th>SMILES</th>
<th>Example Prioritization Scheme (PBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57-74-9</td>
<td>1,2,4,5,6,7,8-octachloro-2,3,3a,4,7,7a-h</td>
<td>ClC1CC2C(C1Cl)C1(Cl)C(Cl)=C(Cl)C2(Cl)C1(Cl)Cl</td>
<td>P;vB;vT</td>
</tr>
</tbody>
</table>

The file can be open as an Excel sheet.