



# QSARINS-Chem

Standalone Version

## Quick Start Guide



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## Information about the Standalone Version

### Models

This standalone version of QSARINS-Chem contains QSAR models for the prediction of:

| Category   | Model   |
|--|---|
| 1. Physico-Chemical properties                       | 1. Soil Organic Carbon-Water partition Coefficient ( $K_{oc}$ )   |
| 2. Global Indexes                                    | 1. Global Half-Life Index<br>2. Insubria PBT Index  |
| 3. Aquatic Toxicity                                  | 1. Fish Acute Toxicity ( <i>P.promelas</i> )  |
| 4. Aquatic Toxicity of Personal Care Products (PCPs) | 1. PCP Freshwater Algae Growth Inhibition<br>2. PCP <i>Daphnia</i> sp. Acute Toxicity<br>3. PCP Fish Acute Toxicity Model 1 (logP based)<br>4. PCP Fish Acute Toxicity Model 2<br>5. PCP Aquatic Toxicity Index (ATI)   |
| 5. Aquatic Toxicity of Pharmaceuticals               | 1. Pharmaceutical Freshwater Algae Growth inhibition<br>2. Pharmaceuticals <i>Daphnia</i> sp. acute Toxicity<br>3. Pharmaceuticals fish Acute Toxicity ( <i>O.mykiss</i> )<br>4. Pharmaceuticals fish Acute Toxicity ( <i>P.promelas</i> )<br>5. Pharmaceuticals Aquatic Toxicity Index (ATI) |
| 6. Metabolic transformation in fish                  | 1. Fish Biotransformation Model 1<br>2. Fish Biotransformation Model 2<br>3. Fish Biotransformation Model 3   |
| 7. Metabolic transformation in human                 | 1. Human biotransformation Model 1<br>2. Human biotransformation Model 2<br>3. Human biotransformation Model 3<br>4. Human biotransformation Model 4<br>5. Human Total elimination  |

## Database

This standalone version of QSARINS-Chem contains the database published by Gramatica et al. 2014<sup>1</sup> which includes the following datasets:

| Chemical Class                 | Endpoint-Type                  | Dataset Name  |
|--------------------------------|--------------------------------|---|
| 1. General                     | 1. Physico-Chemical Properties | 1. Soil Organic Carbon-Water partition Coefficient ( $K_{oc}$ )   |
|                                | 2. Environmental Persistence   | 1. Sediment Half-Lives<br>2. Soil Half-Lives<br>3. Water Half-Lives<br>4. Air Half-Lives<br>5. NO <sub>3</sub> reactivity<br>6. O <sub>3</sub> reactivity<br>7. OH reactivity<br>8. Global Half-Life Index      |
|                                | 3. Bioconcentration Factor     | 1. BCF-Fernandez<br>2. BCF-Lu   |
|                                | 4. Metabolic Transformation    | 1. Fish Biotransformation<br>2. Human Biotransformation Model 1<br>3. Human Biotransformation Model 2<br>4. Human Biotransformation Model 3<br>5. Human Biotransformation Model 4<br>6. Human Total Elimination |
|                                | 5. Aquatic Toxicity            | 1. Fish acute toxicity ( <i>P.promelas</i> )  |
|                                | 6. Endocrine Disruption        | 1. Estrogen Receptor Binding  |
| 2. Aromatic Amines             | 1. Mutagenicity                | 1. Aromatic Amines mutagenicity TA98<br>2. Aromatic Amines mutagenicity TA100   |
| 3. (Benzo)Triazoles            | 1. Physico-Chemical Properties | 1. (B)TAZ Kow<br>2. (B)TAZ Solubility in Water<br>3. (B)TAZ Vapor Pressure<br>4. (B)TAZ Melting Point   |
|                                | 2. Aquatic Toxicity            | 1. (B)TAZ Algae acute toxicity ( <i>P.subcapitata</i> )<br>2. (B)TAZ <i>Daphnia sp</i> acute toxicity<br>3. (B)TAZ Fish acute toxicity ( <i>O.mykiss</i> )  |
| 4. Brominated Flame Retardants | 1. Physico-Chemical Properties | 1. BFR Kow<br>2. BFR Koa<br>3. BFR Vapor Pressure<br>4. BFR Solubility in Water<br>5. BFR Henry Law Constant<br>6. BFR Melting Point  |
|                                | 2. Endocrine Disruption        | 1. BFR-DR-Ag<br>2. BFR-ER-Ag<br>3. BFR-ERODind<br>4. BFR-PR-ant   |

| Chemical Class                               | Endpoint-Type                  | Dataset Name  |
|--|--------------------------------|---|
|  |                                | 5. BFR-SULT-REP<br>6. BFR-T4-REP<br>7. BFR Receptor Binding Affinity  |
| 5. Dioxin Analogues                          | 1. Biological Activity         | 1. Dioxin Analogues pAHH<br>2. Dioxin Analogues pRB   |
| 6. Esters                                    | 1. Physico-Chemical Properties | 1. Esters Flash Point   |
|  | 2. Aquatic Toxicity            | 1. Esters Algae acute toxicity<br>2. Esters <i>Daphnia sp</i> acute toxicity<br>3. Esters Fish acute toxicity ( <i>P.promelas</i> )<br>4. Esters Aquatic Toxicity Index (EATIN)                                   |
| 7. Fragrances                                | 1. Terrestrial Toxicity        | 1. Fragrances Oral toxicity (Rat)   |
|  | 2. Biochemical activity        | 1. Fragrances Inhibition NADHox<br>2. Fragrances Mitochondrial memb pot   |
| 8. Nitrated polycyclic aromatic hydrocarbons | 1. Mutagenicity                | 1. NitroPAH mutagenicity TA100  |
| 9. Perfluorinated Compounds                  | 1. Physico-Chemical Properties | 1. PFC Critical Micelle Concentration<br>2. PFC Solubility in Water<br>3. PFC Vapor Pressure  |
|  | 2. Terrestrial Toxicity        | 1. PFC Oral toxicity (Rat)<br>2. PFC Oral toxicity (Mouse)<br>3. PFC Inhalation toxicity (Rat)<br>4. PFC Inhalation toxicity (Mouse)  |
| 10. Personal Care Products                   | 1. Aquatic Toxicity            | 1. PCP Algae acute toxicity ( <i>P.subcapitata</i> )<br>2. PCP <i>Daphnia sp</i> acute toxicity<br>3. PCP Fish acute toxicity ( <i>P.promelas</i> )   |
| 11. Pharmaceuticals                          | 1. Aquatic Toxicity            | 1. Pharm. Algae acute toxicity ( <i>P.subcapitata</i> )<br>2. Pharm. <i>Daphnia sp</i> acute toxicity<br>3. Pharm. Fish acute toxicity ( <i>O.mykiss</i> )<br>4. Pharm. Fish acute toxicity ( <i>P.promelas</i> ) |

**NOTE ABOUT DATA AND STRUCTURES:** All the chemical structures have been designed and “energetically minimized” (AM1 method in HyperChem v.7.03) by the QSAR Research Unit in Environmental Chemistry and Ecotoxicology at the University of Insubria<sup>1</sup>. SMILES (not in the canonical form) reported in the database have been generated from the 3D structures using OpenBabel v 2.3.2. All the experimental data have been collected from literature. Information about original data, data collection and curation can be found in the publications cited in the database. No experimental data have been generated by QSAR Research Unit in Environmental Chemistry and Ecotoxicology at the University of Insubria (exceptions are the global indexes generated by Principal Component Analysis).

<sup>1</sup> “QSARINS-chem: Insubria datasets and new QSAR/QSPR models for environmental pollutants in QSARINS”, Gramatica P., Cassani S., Chirico N. Journal of Computational Chemistry 2014, 35, 1036-1044. DOI: 10.1002/jcc.23576

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## How to cite:

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We would also appreciate citations to the website: <http://dunant.dista.uninsubria.it/qsar/>

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## Overview

QSARINS-Chem allows the user to input his molecular structures and get estimations and Applicability Domain for a desired QSAR model.

Minimal information required to obtain prediction are:

-Chemical structures files (e.g. .smi, .mol) (see below to see how to set a .smi file)

## Tutorial

### Step 1: Select the model:

1) **Run** QSARINS-Chem.jar (usually by double clicking on its icon. If it is not working, please ask your IT staff because it depends on whether, or how, the Java environment is configured on your machine). The first time you execute QSARINS-Chem, you need to read the Licence agreement and if you agree, by selecting “I agree”, you can use QSARINS-Chem.



Figure 1. Licence agreement

2) The “Model Selection” page will open; here **you can select** the desired **QSAR model** from the blue drop-down menu. Once selected, the main page summarizes the principal information of the selected model (model’s description, equation and statistics).

**As a practical tutorial, select “Fish biotransformation model 1”, as shown in Figure 2. The endpoint of this model is “logHLn (days)”, that is “the base-10 logarithm of the whole-body biotransformation half-life of chemicals in fish in days normalized for a reference 10g fish at a water temperature of 288K”. This model will be used in the following steps as a tutorial (which is highlighted in this color).**

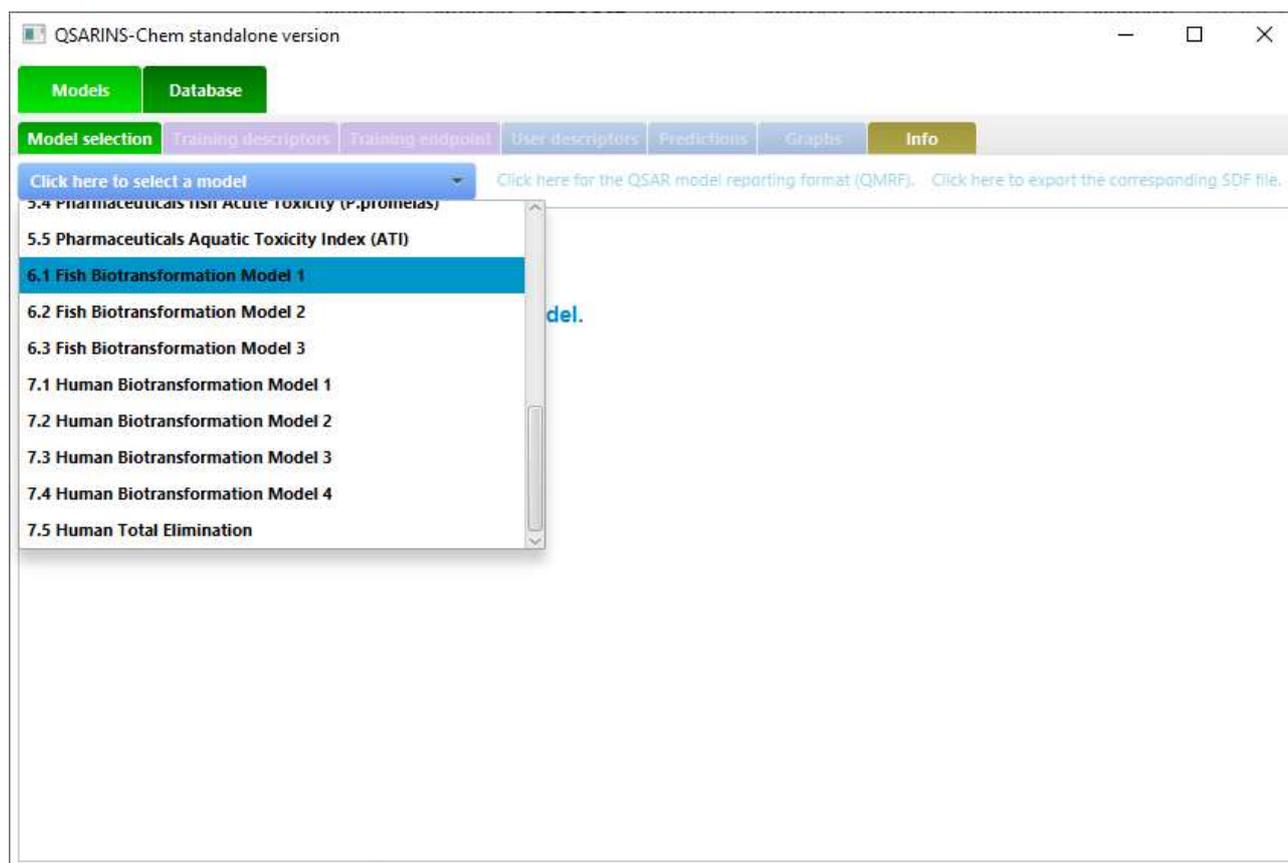


Figure 2. Model selection

3) Once the model is selected, two tabs (“Training descriptors”, Figure 3, and “Training endpoint”, Figure 4) are activated in order to provide information about the Training set used for the model development:

The “Training descriptors” tab shows the values of the training set descriptors of the selected QSAR model. These values can be used, as a reference, to check the validity of the descriptors values calculated for the new molecules, i.e. those provided by the user (see Step 2).

The “Training endpoint” tab shows the experimental and estimated endpoint for the training set objects as well as the residuals and the leverage values (i.e. the diagonal elements of the Hat matrix). Outliers for the response and influential objects are highlighted in red. These values can be used as a reference for checking the validity of the predictions (see Step 3 for further information).

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Models Database

Model selection Training descriptors Training endpoint User descriptors Predictions Graphs Info

| No. | Name        | Exp | VAdjMat | nHBacc | nX | SaaC | PubchemFP503 | PubchemFP25 |
|-----|-------------|-----|---------|--------|----|------|--------------|-------------|
| 1   | XXXUNK-46-1 | 11  | 5.5     | 3      | 0  | 0    | 0            | 0           |
| 2   | XXXUNK-46-2 | 8.6 | 6.2     | 9      | 0  | 0    | 0            | 0           |
| 3   | XXXUNK-46-3 | 11  | 5.5     | 3      | 0  | 0    | 0            | 0           |
| 4   | XXXUNK-46-4 | 13  | 6       | 0      | 8  | 0    | 0            | 0           |
| 5   | XXXUNK-46-5 | 13  | 6.1     | 0      | 8  | 0    | 0            | 0           |
| 6   | XXXUNK-46-6 | 13  | 6.1     | 0      | 8  | 0    | 0            | 0           |
| 7   | XXXUNK-46-7 | 13  | 5.4     | 0      | 4  | 0    | 0            | 0           |
| 8   | XXXUNK-46-8 | 13  | 5.4     | 0      | 4  | 0    | 0            | 0           |
| 9   | XXXUNK-46-9 | 13  | 5.3     | 0      | 4  | 0    | 0            | 0           |
| 10  | 018936-52-2 | 9   | 5       | 3      | 1  | 0    | 1            | 0           |
| 11  | 093703-48-1 | 6   | 5.1     | 0      | 4  | 0    | 0            | 0           |
| 12  | 189084-61-5 | 6   | 5.1     | 0      | 4  | 0    | 0            | 0           |
| 13  | 068631-49-2 | 6.4 | 5.2     | 0      | 6  | 0    | 0            | 0           |
| 14  | 000050-29-3 | 2.4 | 5.2     | 0      | 5  | 0    | 1            | 0           |
| 15  | 000050-32-8 | 2.3 | 5.3     | 0      | 0  | 11   | 0            | 0           |
| 16  | 000053-19-0 | 2.4 | 5.2     | 0      | 4  | 0    | 1            | 0           |
| 17  | 000053-70-3 | 2.3 | 5.5     | 0      | 0  | 11   | 0            | 0           |
| 18  | 000055-38-9 | 6   | 5       | 2      | 0  | 0    | 0            | 0           |

Figure 3. Training descriptors used for model development

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Models Database

Model selection Training descriptor Training endpoint User descriptors Predictions Graphs Info

| No. | Name        | Exp     | Estimated endpoint | HAT $\hat{v}_i$ ( $h^* = 4.7e-02$ ) | Residual |
|-----|-------------|---------|--------------------|-------------------------------------|----------|
| 1   | XXXUNK-46-1 | 0.34    | -0.45              | 1.3e-02                             | -0.79    |
| 2   | XXXUNK-46-2 | -0.61   | -0.42              | 7.6e-02                             | 0.19     |
| 3   | XXXUNK-46-3 | 8.1e-02 | -0.45              | 1.3e-02                             | -0.53    |
| 4   | XXXUNK-46-4 | 2.6     | 1.7                | 3.2e-02                             | -0.93    |
| 5   | XXXUNK-46-5 | 1.7     | 1.8                | 3.3e-02                             | 0.10     |
| 6   | XXXUNK-46-6 | 2.4     | 1.8                | 3.3e-02                             | -0.68    |
| 7   | XXXUNK-46-7 | 0.36    | 0.60               | 1.8e-02                             | 0.24     |
| 8   | XXXUNK-46-8 | 0.4     | 0.60               | 1.8e-02                             | 0.20     |
| 9   | XXXUNK-46-9 | 0.29    | 0.54               | 1.7e-02                             | 0.25     |
| 10  | 018936-52-2 | 0.65    | 0.18               | 1.3e-02                             | -0.47    |
| 11  | 093703-48-1 | 2.3     | 1.1                | 6.1e-03                             | -1.1     |
| 12  | 189084-61-5 | 1.4     | 1.1                | 6.1e-03                             | -0.29    |
| 13  | 068631-49-2 | 2       | 1.5                | 1.1e-02                             | -0.51    |
| 14  | 000050-29-3 | 1.9     | 2.3                | 8.5e-03                             | 0.36     |
| 15  | 000050-32-8 | 4.7e-02 | 0.15               | 5.7e-02                             | 0.11     |
| 16  | 000053-19-0 | 1.7     | 2.1                | 8.3e-03                             | 0.44     |
| 17  | 000053-70-3 | 0.21    | 0.33               | 5.4e-02                             | 0.12     |
| 18  | 000055-38-9 | -0.36   | 0.25               | 5.5e-03                             | 0.61     |

Figure 4. Endpoint values used for model development and related additional information



an example of calculated descriptors). **Note: QSARINS-Chem cannot process molecules with missing descriptors; in this case you have to manually enter the value or delete the chemical (right click and press delete).**

| No. | Name                  | gmax      | VAdjMat     | nHBacc     | nX      | SaaaC    | PubchemFP503    | PubchemFP29     | minHBd      | ndsCH     | logHLn (days) | Status   |
|-----|-----------------------|-----------|-------------|------------|---------|----------|-----------------|-----------------|-------------|-----------|---------------|----------|
| 1   | Pyrene                | 2.2       | 5           | 0          | 0       | 8.1      | 0               | 0               | 0           | 0         | 0.32          | OK       |
| 2   | BaP                   | 2.3       | 5.3         | 0          | 0       | 11       | 0               | 0               | 0           | 0         | 4.7e-02       | OK       |
| 3   | Methoxychlor          | 5.3       | 5.4         | 0          | 3       | 0        | 0               | 0               | 0           | 0         | Optional      | OK       |
| 4   | Deltamethrin          | 13        | 5.8         | 3          | 2       | 0        | 0               | 0               | 0           | 1         | 0.51          | OK       |
| 5   | 4-nonyl-phenol        | 9.1       | 5           | 0          | 0       | 0        | 0               | 0               | 0.61        | 0         | -0.23         | OK       |
| 6   | Cyclohexyl-salicylate | 12        | 5           | 2          | 0       | 0        | 0               | 0               | 0.57        | 0         | Optional      | OK       |
| 7   | Tetrahydropyrene      | 2.3       | 5           | 0          | 0       | 0        | 0               | 0               | 0           | 0         | Optional      | OK       |
| 8   | 1-Chloromethylpyrene  | 2.3       | 5.2         | 0          | 1       | 8.4      | 0               | 0               | 0           | 0         | Optional      | OK       |
| 9   | 1-Aminopyrene         | 6.1       | 5.1         | 1          | 0       | 7.6      | 0               | 0               | 0.47        | 0         | Optional      | OK       |
| 10  | Decafluoro-pyrene     | 14        | 5.7         | 0          | 10      | -9.5     | 0               | 0               | 0           | 0         | Optional      | Warning  |
| 11  | Type name here        | Type v... | Type val... | Type va... | Type... | Type ... | Type value here | Type value here | Type val... | Type v... | Optional      | Empty... |

Figure 6. Descriptors values calculated for user-entered molecules

**In the example of this tutorial (see Figure 6) four experimental values of the endpoint (“logHLn (days)”) have been manually entered. These values are optional, but when provided they help to evaluate the reliability of the predictions.**

3) Press “Apply Model” to run the model and generate predictions.

### Step 3: get estimated values and evaluate the applicability domain

Once the model is applied, the “Predictions” tab will be activated (see Figure 7). This tab contains, in addition to the ID number and the molecule names, the following information:

- 1) **Experimental endpoint.** This information is optional, see Step 2 for further information.
- 2) **Estimated endpoint.** This is the **endpoint predicted by the model** of the user-entered molecules. The prediction of the endpoint is the aim of using QSARINS-Chem.
- 3) **HAT values (leverages).** These values represent the “distance of the molecular structures” of the molecules entered by the user, respect to the ones used for the model development. When the HAT value of the user-entered molecules is above the calculated threshold ( $h^*$ ) that means they could be structurally different from the ones used for the development of the model. These molecules need further checking. **An example of this check is shown in the following Step 4: graphical inspection.**

- 4) **Residual and standardized residuals.** These values are a measure of the distance between the predicted and the experimental values, if the user provides the latter. The smaller the residual, the lower the error in prediction.
- 5) **Status.** If problems are detected, the status is displayed as “Warning” in red. Moving the mouse pointer on the red value/s (e.g. 26 or 9.2e-02 of the tenth molecule in the example of Figure 7) on the same row a tooltip will appear indicating the reason of the problem.

| No. | Name                  | Experimental endpoint | Estimated endpoint | HAT i/i (h* = 4.7e-02) | Residual     | Standardized residual   | Status  |
|-----|-----------------------|-----------------------|--------------------|------------------------|--------------|-------------------------|---------|
| 1   | Pyrene                | 0.32                  | 0.13               | 3.2e-02                | -0.19        | -0.33                   | OK      |
| 2   | BaP                   | 4.7e-02               | 0.15               | 5.7e-02                | 0.11         | 0.19                    | Warning |
| 3   | Methoxychlor          | Not provided          | 1.5                | 7.5e-03                | Need expe... | Need experimental en... | OK      |
| 4   | Deltamethrin          | 0.51                  | 0.47               | 1.6e-02                | -3.8e-02     | -6.6e-02                | OK      |
| 5   | 4-nonyl-phenol        | -0.23                 | -0.20              | 1.8e-02                | 2.8e-02      | 4.8e-02                 | OK      |
| 6   | Cyclohexyl-salicylate | Not provided          | -0.87              | 1.1e-02                | Need expe... | Need experimental en... | OK      |
| 7   | Tetrahydropyrene      | Not provided          | 1.1                | 8.8e-03                | Need expe... | Need experimental en... | OK      |
| 8   | 1-Chloromethylpyrene  | Not provided          | 0.38               | 3.4e-02                | Need expe... | Need experimental en... | OK      |
| 9   | 1-Aminopyrene         | Not provided          | -0.69              | 3.5e-02                | Need expe... | Need experimental en... | OK      |
| 10  | Decafluoro-pyrene     | Not provided          | 2.6                | 9.2e-02                | Need expe... | Need experimental en... | Warning |

Figure 7. Endpoint predictions for user-entered molecules

You can **select** the chemicals of your interest and **right click to copy** the predictions. **Paste** in “Excel” or in other format to save the estimations.

#### Step 4: graphical inspection

To visualize the graphs for the estimation of the predicted values performances, **select the “Graphs” tab** and then **press the “Calculate graphs”** button. The following graphs (Figures 8-11) will be displayed.

**1) Insubria Graph:** plot of HAT values (leverages) (see also point 3 in Step 3) vs. estimated values of the model. The red points (Training) are the predicted values of the molecules endpoint used for the model development, the light blue dots (User Set N) the user-entered molecules without the experimental value (optional) while the blue dots (User Set E) are the ones with the experimental value.

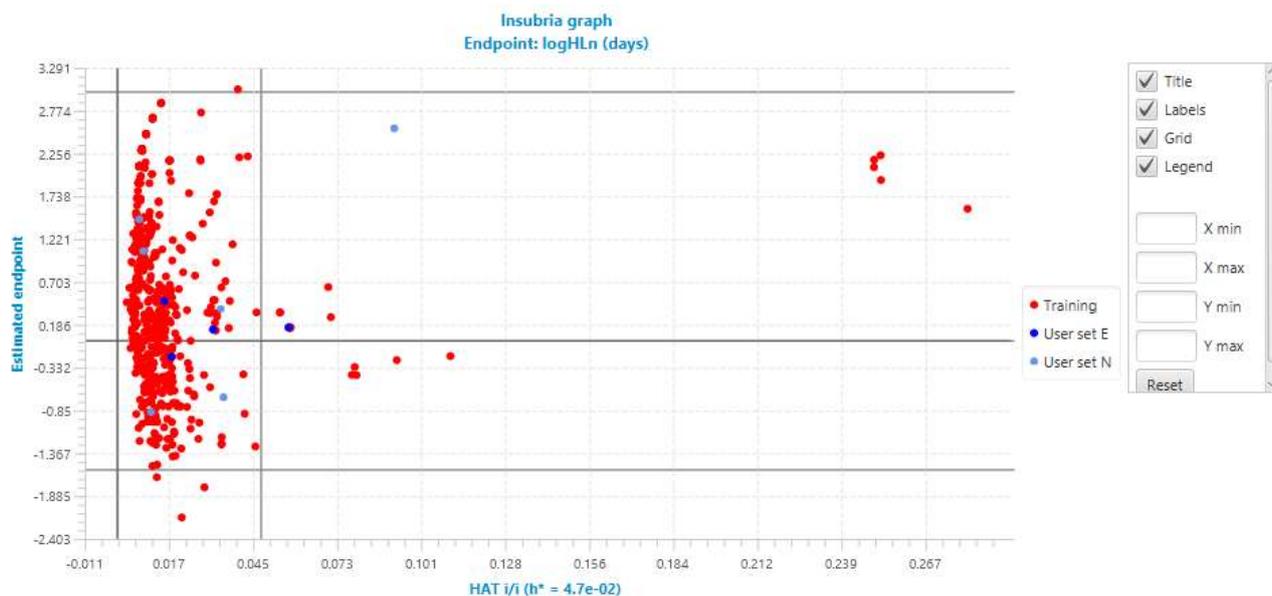


Figure 8. Insubria graph

**2) Experimental vs. Estimated values.** This plot provides visual information of the fitting of the model (Training, red points). If experimental values are provided by the user-entered molecules, they will appear in this graph (User set, blue points). *In the example of this tutorial, see Figure 9, all blue dots are within the scatter plot of the training set (red dots). That means that the user-entered molecules predictions are within the experimental and predictivity domain of the model. In case they are outside, further checking of user-entered molecules should be performed.*

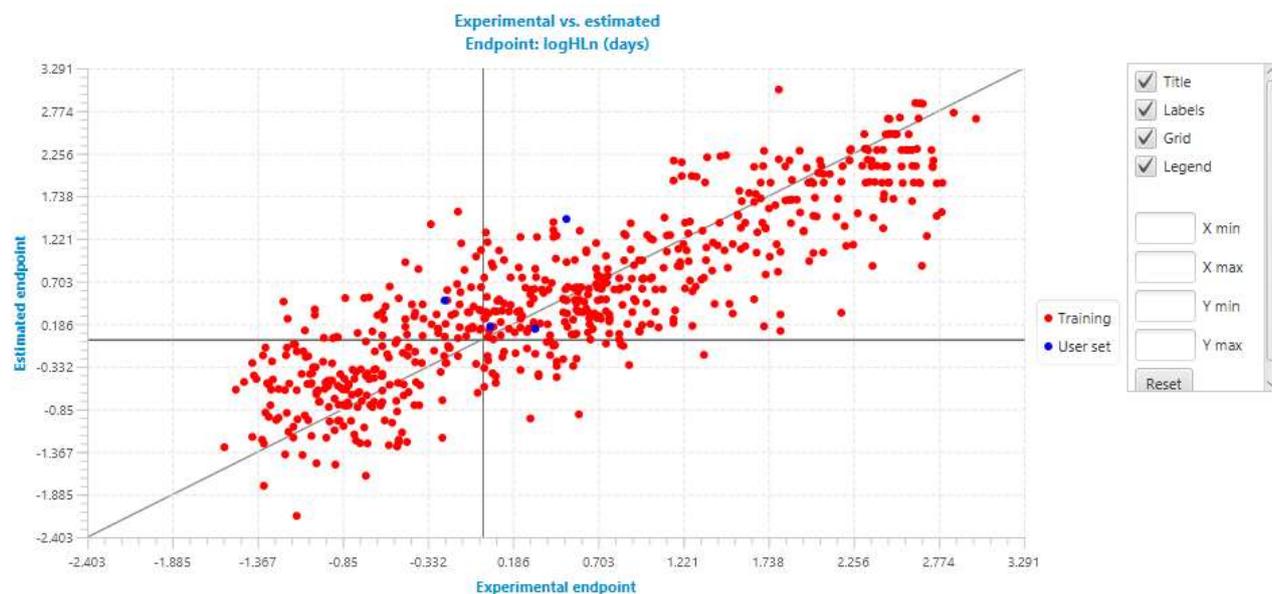


Figure 9. Experimental vs. estimated endpoints

**3) Residuals.** This graph works similarly to the previous one (“Experimental vs Estimated values”) but shows residuals instead. It is commonly used to evaluate the appropriateness of using a linear model. When used

on user-entered data, the blue points (User set) should fall within the range of dispersion of the red points (Training).

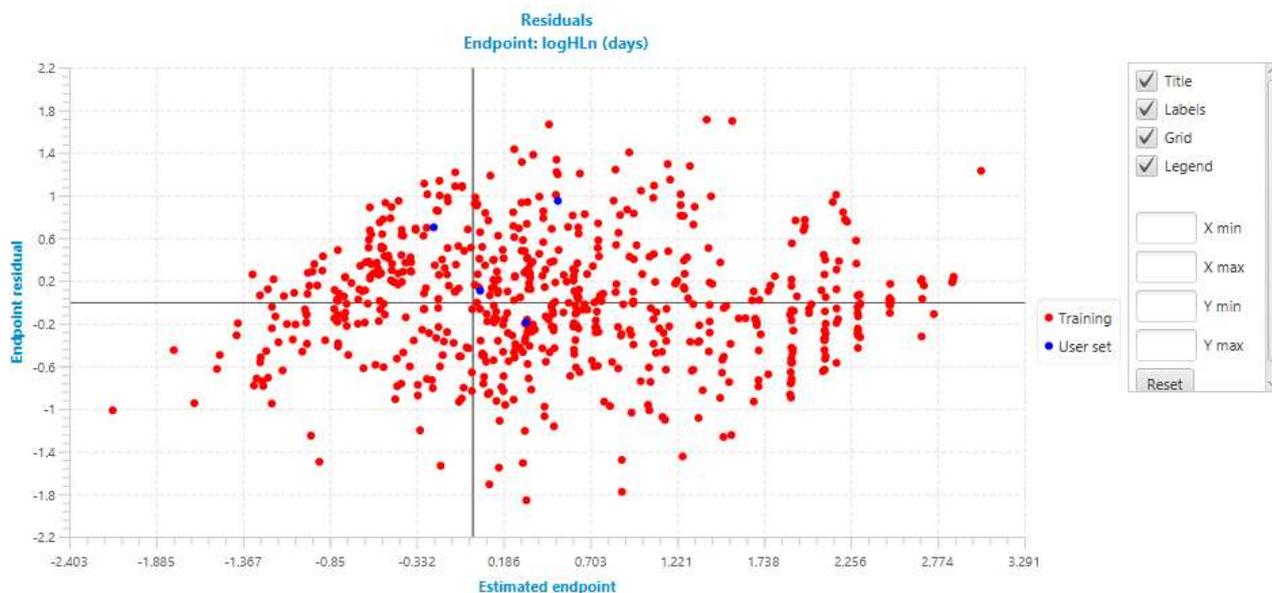


Figure 10. Endpoint residual

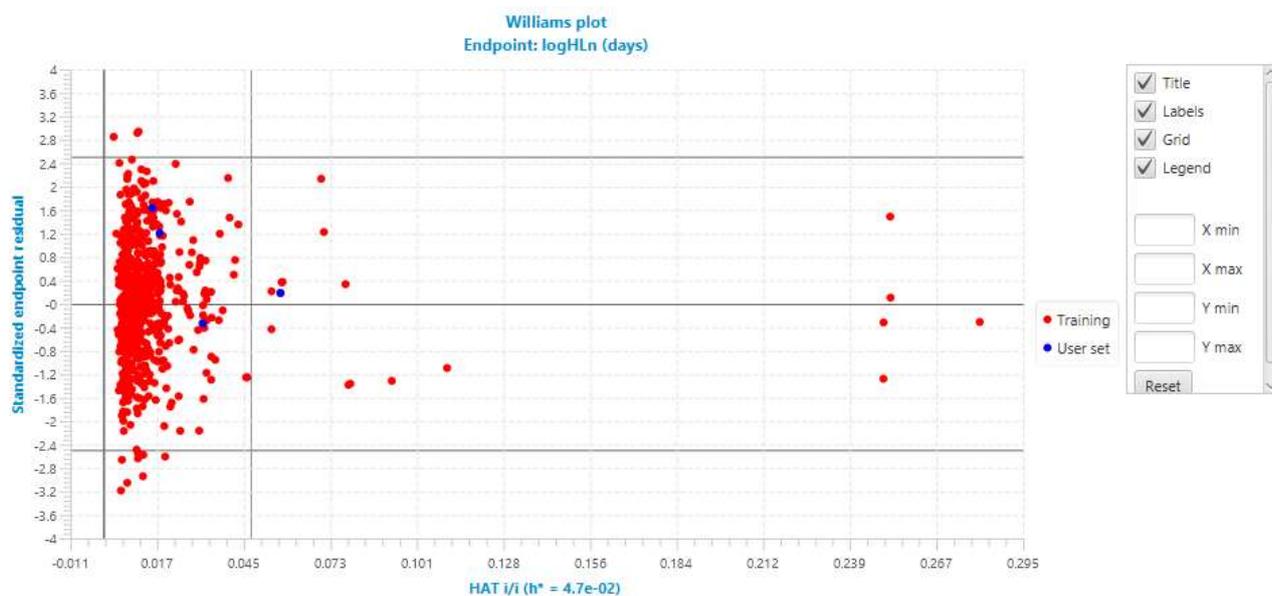


Figure 11. Williams plot.

**4) Williams plot.** This graph is similar to the Insubria Graph. The difference is in the ordinate axis that reports the standardized residuals of the responses. The Insubria Graph allows for the visualization of “User set” chemicals in the applicability domain defined by leverage distance and experimental range of the related model. Differently, the Williams graph plots the leverage distance vs. standardized residuals. Therefore, the user-entered molecules (blue dots) must be provided with the experimental values otherwise the residual cannot be calculated. The use of the residuals helps in better evaluating the reliability of the predictions.

**Note:** you can copy and paste or save any of these graphs.

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## How to set up a SMILES structural file (.smi)

PaDEL-Descriptor software can calculate descriptors from SMILES placed in a **.smi** structural file. This is a “tab delimited” text file containing the **SMILES structures in the first column** and the Identifiers (optional) in the second column, **no header**. The extension of file must be **.smi**

To generate this file in “Excel” (or similar software):

- 1) **Open** an empty document
- 2) **Paste** your SMILES in the first column
- 3) If present, **paste** the identifier (ID or CAS or NAME) in the second column
- 4) If present, **delete** the header
- 5) **Save** as tab delimited text file [**TEXT (tab delimited)(\* .txt)**]
- 6) Manually **change** the extension from **.txt** to **.smi**

*(To see file extension on*

**Windows 7:** *Open Windows Explorer and click the **Organize** button towards the top left. Choose **Folder and search options** from the menu. Click the **View** tab in the window that opens, then scroll down and untick the box next to **'Hide file extensions for known file types'***

**Windows 8/10:** *open a **File Explorer** window (the new name for Windows Explorer) and click the **View** tab.*

**Mac:** *Click on the **Finder** menu and select **Preferences**. Select **Advanced** button and put a check mark in the checkbox labeled **Show all filename extension**)*

- 7) **Place** the file in an empty folder to use in **Step 2 point 3**