



What is new in Toolbox 4.5?

Presenters:

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QSAR Toolbox

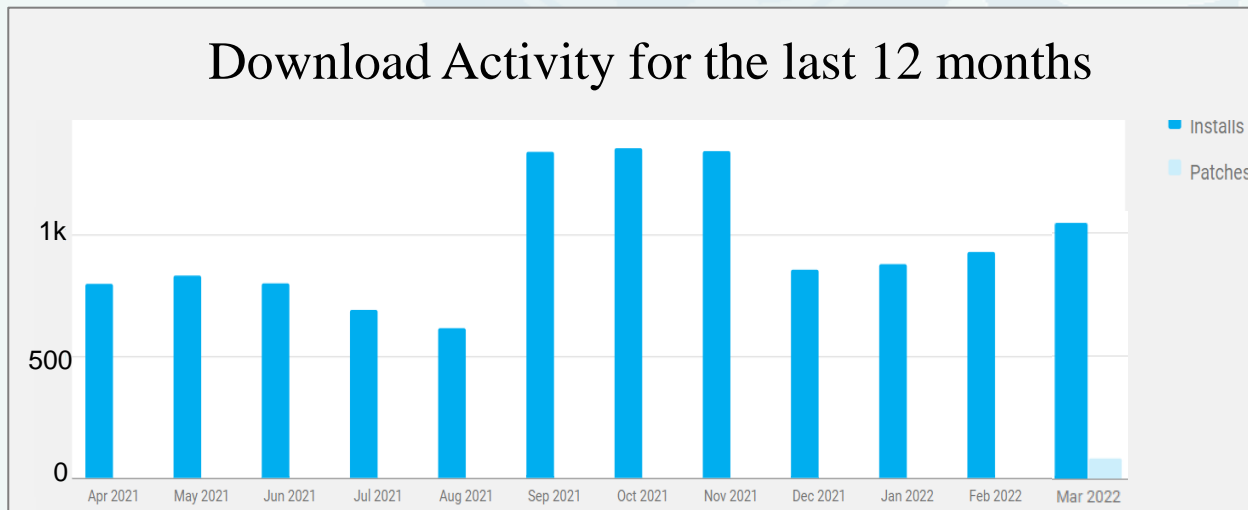
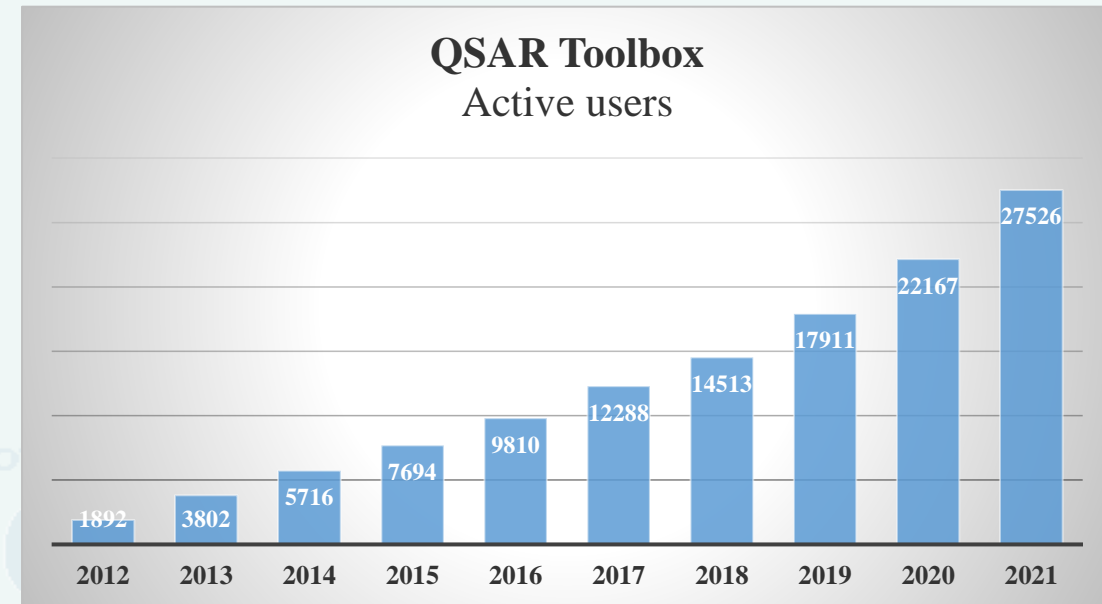
History

- Initiated as a proof-of-concept in 2006
- Version 1.0 released in October 2008
- Latest public version: 4.5 released in October 2021
- Update of version 4.5 – 4.5SP1 released in March 2022

QSAR Toolbox

Statistics

- Active users: 27 796
- Toolbox 4.x downloads: 25 761
- Toolbox 4.5 downloads: 4 839



Live statistics here: <https://qsartoolbox.org/download/statistics/>

What is new in QSAR Toolbox v.4.5?



General:

➤ **Web client**

Providing basic features known from the Simplified UI along with a dedicated module for searching in imported IUCLID databases

Important new functionalities/improvements:

➤ **Substance information & IUCLID compatibility**

*Import/export data from(to) IUCLID to(from) Toolbox;
Searching capabilities allowing composition search in IUCLID databases*

➤ **Workflow editor (WE)**

A feature of Toolbox which helps the user define their own (custom) automated workflow schemes for predicting or grouping of chemicals.

➤ **Automated workflow for DASS**

A workflow for searching for analogues and read-across, which automatically controls the Toolbox stages and finishes with a prediction for skin sensitization that could be used in a defined approach for skin sensitization (DASS)

Additional new features/improvements:

- New form for easier definition of the target endpoint – following the endpoint tree organization;
- Possibility to define additional endpoints, relevant to the target endpoint;
- Creating custom calculator using experimental data;
- Caching of generated metabolites in Toolbox database;
- Installation of external modules without administrative rights;
- Preparing of additional user manual for the Workflow editor;
- etc.

Resources:

- 10 updated databases & 1 updated inventory;
- 2 new databases;
- 28 updated profilers;
- 12 updated metabolic simulators.

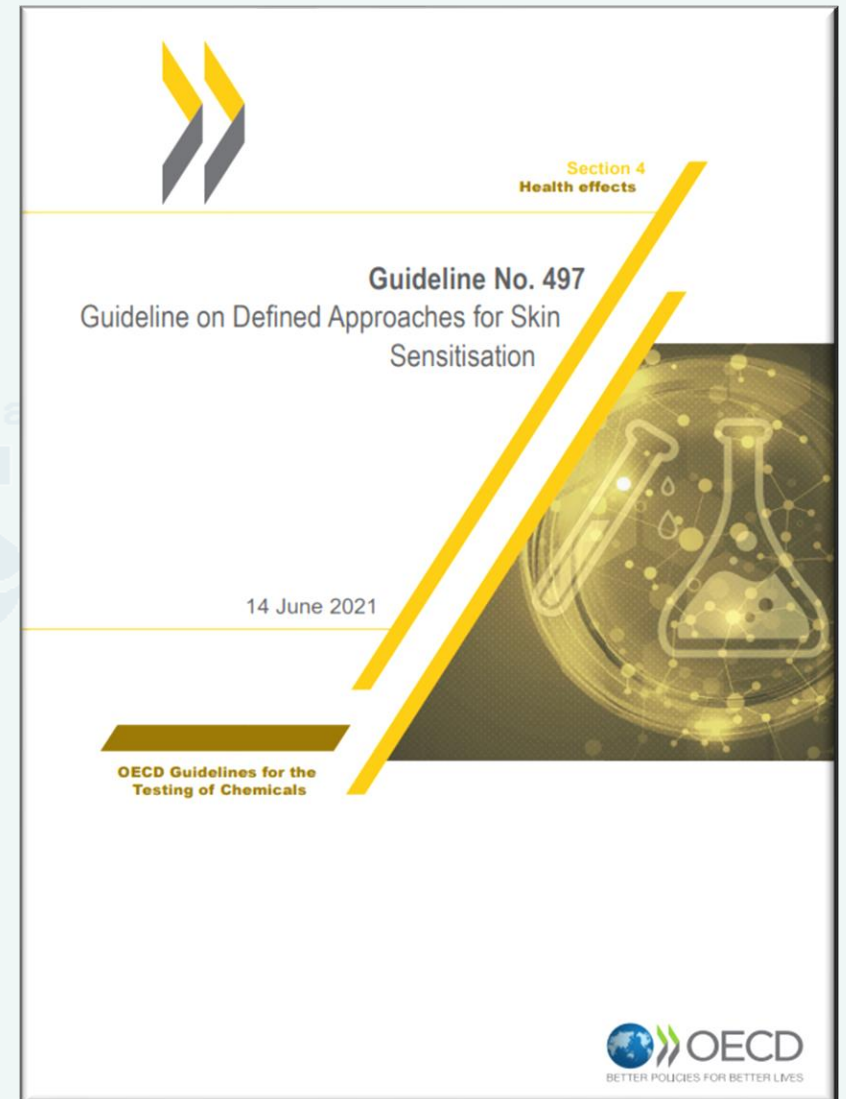
See the full list with *What is new in QSAR Toolbox v.4.5* here: <https://qsartoolbox.org/wp-content/uploads/2021/09/Toolbox-4.5-Release-Notes.pdf>

Automated workflow for defined approaches for skin sensitization (DASS AW)



DASS – Introduction:

- OECD Test Guideline on Defined Approaches on Skin Sensitisation (DASS) has been published (OECD TG 497).
- This is the first guideline that uses non-animal methods to predict whether a chemical can cause skin allergies.
- Three DAs are currently included.
- One of the DAs - *Integrated Testing Strategy (ITS) v.2* uses predictions from *OECD QSAR Toolbox*, obtained by a specifically created automated workflow (DASS AW)



Guideline No. 497: Defined Approaches on Skin Sensitisation: <https://doi.org/10.1787/b92879a4-en>

DASS AW - implementation

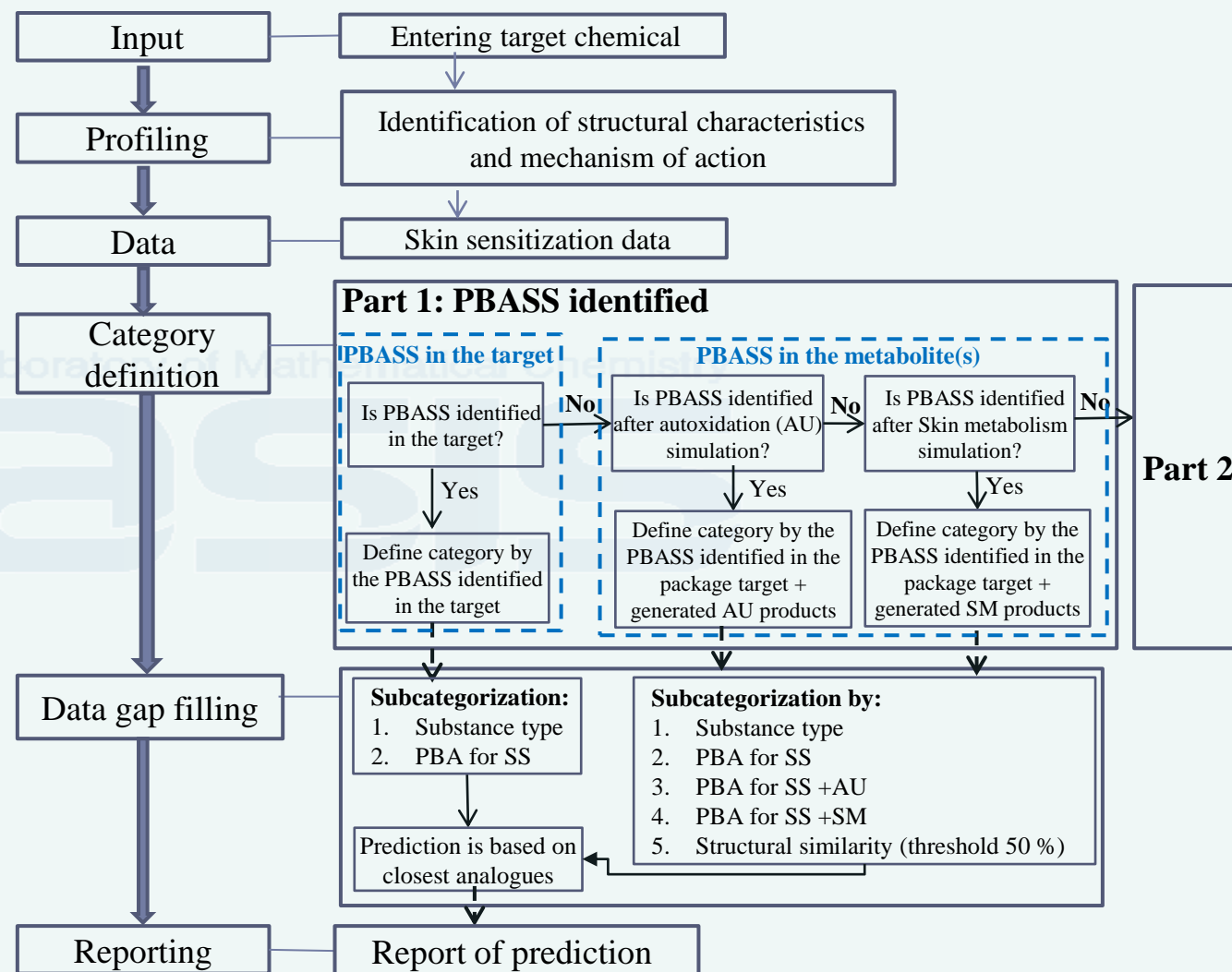
- The WE has been used for development and implementation of the specific AW for SS predictions, including automated definition of the applicability domain.
- The DASS AW can be used to obtain a prediction for a single target chemical or to be applied in batch mode obtaining predictions for a chemical list.
- The DASS AW is applicable to discrete organic chemicals. It is not applicable to mixtures, salts, UVCBs, polymers, etc.

The screenshot displays the Workflow Editor interface for a workflow titled "EC3 from LLNA or Skin sensitisation from GPMT assays for defined approaches". The interface includes a toolbar with various icons, a "Workflow Tree" on the left, a "Help Panel" on the right, and a "Scenarios" panel at the bottom right. The main workspace shows a flowchart with nodes such as "Start", "PBA identified in the target", "PBA after abiotic activation", "PBA identified after biotic activation", "Prediction", "Apply DASS profiler", "Apply profilers for positive", "Apply profilers for negative", and "Stop". A red circle highlights the "Execute" button in the toolbar. An "Execute workflow" dialog box is open in the foreground, asking: "Would you like to execute the workflow for each chemical in the current list?". The dialog provides three options: "Yes - to apply to each chemical", "No - to apply to the target chemical", and "Cancel - do not do anything".

DASS AW - logic

- The algorithms, implemented in all AWs for predicting skin sensitization are based on the presence/absence of protein binding alert(s) for skin sensitization (PBASS).
- If PBASS is identified in the target as parent or as a result of abiotic or biotic metabolic activation, the AW searches for analogues, acting by the same mechanism

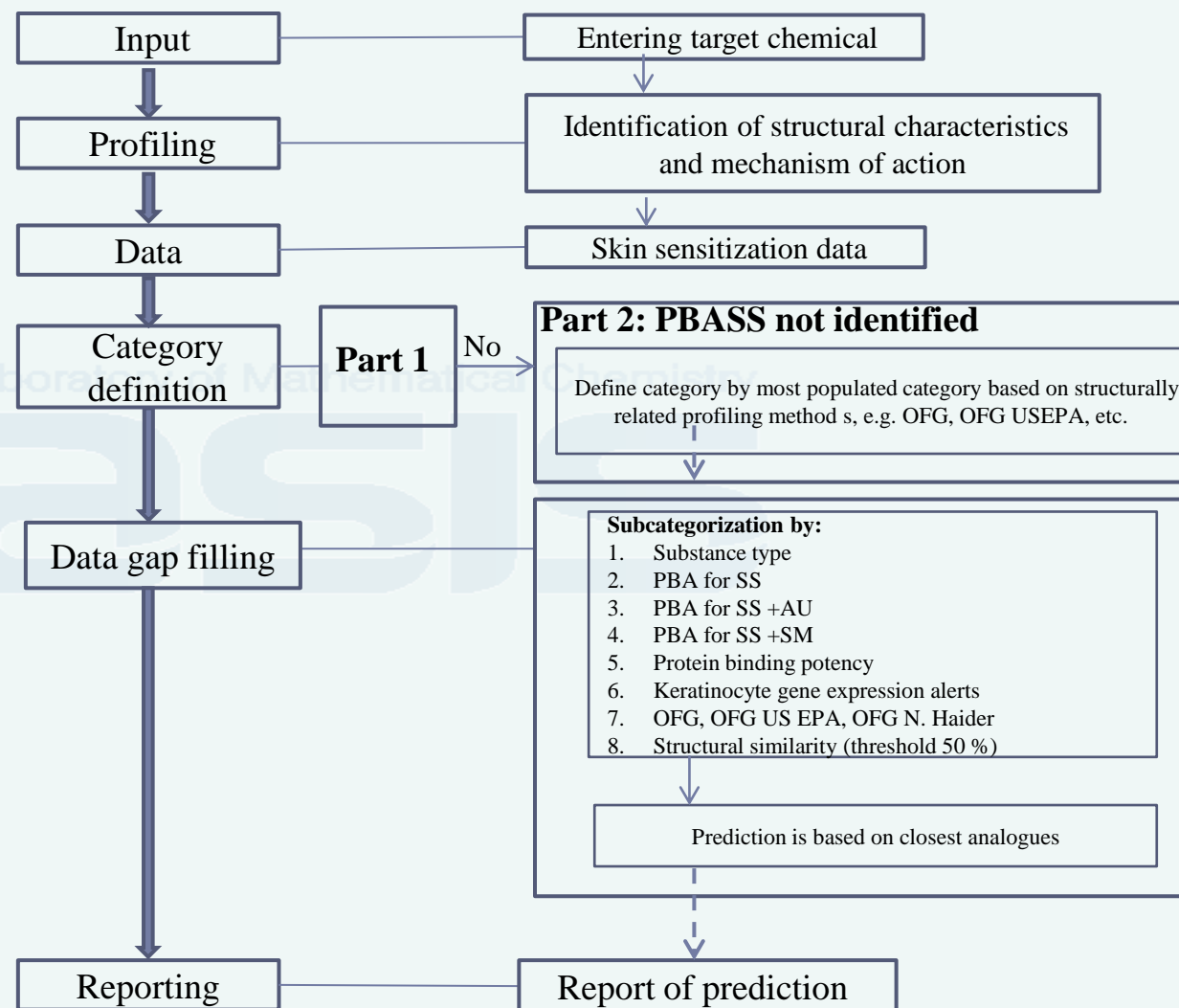
Part 1: Identified protein binding alert(s) for skin sensitization (PBASS) in the target chemical as parent or as a result of metabolic activation



DASS AW - logic

- The algorithms, implemented in all AWs for predicting skin sensitization are based on the presence/absence of protein binding alert(s) for skin sensitization (PBASS).
- If PBASS is identified in the target as parent or as a result of abiotic or biotic metabolic activation, the AW searches for analogues, acting by the same mechanism
- If PBASS is NOT identified in the target as parent or as a result of metabolic activation, the AW searches for structurally similar analogues, having no PBASS
- In case the DASS AW falls to make a prediction by read-across, the prediction is based only on the theoretical knowledge (i.e. PBASS)

Part 2: Protein binding alert(s) for skin sensitization (PBASS) is not identified in the target chemical as parent or as a result of metabolic activation



DASS AW – applicability domain:

- The applicability domain (AD) is automatically defined once the DASS AW finishes with a prediction.
- Three different domain layers (parametric, structural and mechanistic) could be considered depending on the prediction:
 - *structural* and *parametric layers* – based on the structural fragments (atom centered fragments (ACFs)) and phys-chem parameter properties (MW, logKow, VP, WS) of the correctly predicted chemicals from the training set (TS)*
 - *mechanistic layer* – based on the presence/absence of PBASS, identified by the endpoint-specific *Protein binding alerts for skin sensitization by OASIS* profiler, combined with (a)biotic metabolism simulators (*Autoxidation* and *Skin metabolism* simulators)

Toolbox DASS AW outcome		Applicability domain layer		
		Structural	Parametric	Mechanistic
Positive	Read-across	Not considered	Not considered	Considered
	Profiling	Not considered	Not considered	Met by definition
Negative	Read-across	Not considered	Not considered	Considered
	Profiling	Considered	Considered	Met by definition

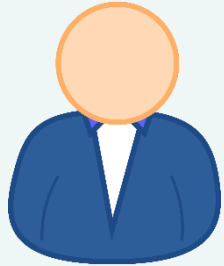
*TS of the DASS AW consists of above 2200 chemicals having SS (LLNA and/or GPMT) experimental data available in the Toolbox Skin sensitization and REACH Skin sensitization (normalized) databases

What is new in Toolbox 4.5?

Toolbox Web Client 2.0

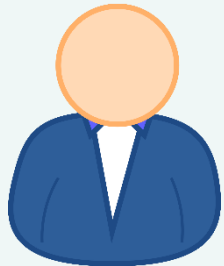
Potential users, new features and deployment scenarios

Toolbox Web Client: Potential users



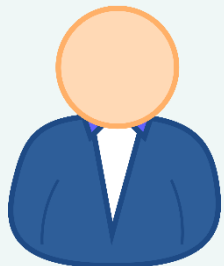
New users (*unfamiliar with Toolbox*)

To get familiar with the basics without being overwhelmed by the full interface



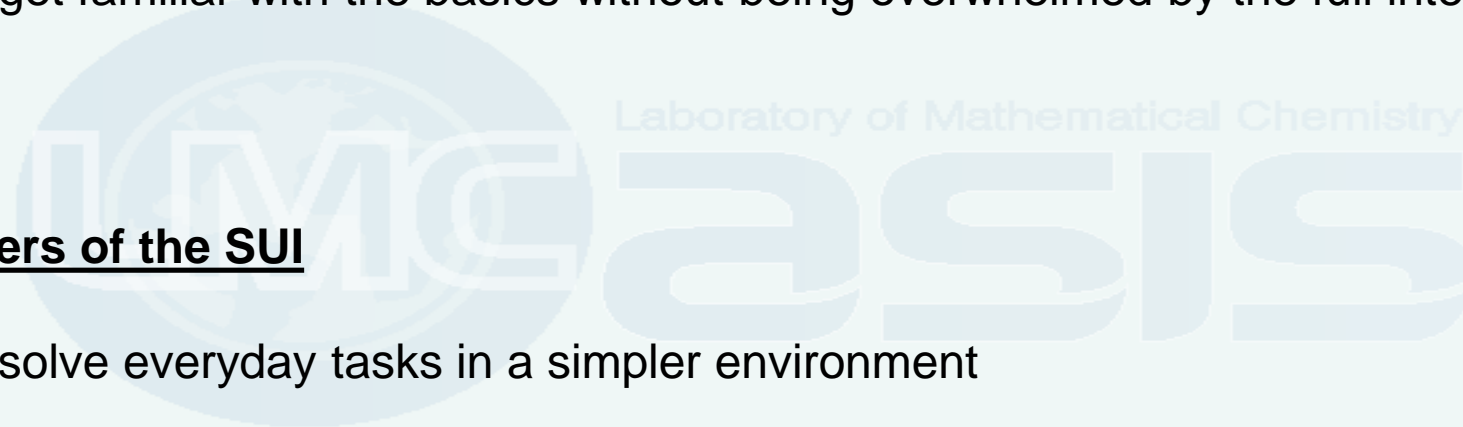
Users of the SUI

To solve everyday tasks in a simpler environment



Regular users (*already experienced with the desktop version*)

To utilize the benefits of a shared deployment and/or mobile usage



Toolbox Web Client: New features

QSAR Toolbox

INPUT

CALCULATE PARAMETERS

APPLY PROFILING

COLLECT DATA

All data ⚡

Specific data

FIND ANALOGUES

RUN WORKFLOWS

RUN QSARs

EXPORT

Search IUCLID databases

v. 2.0.2080a

Type to filter...

Structure info

CAS #	66-25-1	123-72-8
EC Number	200-624-5	204-646-6
Chemical Name(s)	1-hexanal aldehyde C-6 hexaldehyde hexan-1-al Hexanal Hexylaldehyde n-Capronaldehyde	Butanal Butyraldehyde BUTYRALDEHYDE, N- isobutyraldehyde n-butanal n-butyraldehyde
Substance Type	Mono Constituent	Mono Constituent
SMILES	CCCCCC=O	CCCC=O
Parameters		
Physical Chemical Properties		
Boiling point		
Boiling point ^{2/2}	M: 131 °C	M: 74.8 °C
Chemical reactivity		
GSH RC50 ^{2/2}	M: Not reactive at saturation	M: Not reactive at saturation
Melting / freezing point		
Melting point ^{2/2}	M: -56 °C	M: -99 °C
Partition Coefficient:		
N-Octanol/Air		
Log Koa ^{2/2}	M: 4.41	M: 3.39

Real data matrix

Toolbox Web Client: New features

SELECT WORKFLOW

<input type="checkbox"/> EC3 from LLNA or Skin sensitization from GPMT assays for defined approaches (SS AW for DASS)	<input type="checkbox"/>
<input type="checkbox"/> EC3 from LLNA assay	<input type="checkbox"/>
<input type="checkbox"/> EC3 from LLNA or Skin sensitisation from GPMT assays	<input type="checkbox"/>
<input type="checkbox"/> Skin sensitisation from GPMT assay	<input type="checkbox"/>
<input type="checkbox"/> Fish, LC50(EC50) at 96h for Pimephales promelas (mortality)	<input type="checkbox"/>

SELECT QSAR

Endpoints with available QSARs

- > Physical Chemical Properties
- > Environmental Fate and Transport
- > Ecotoxicological Information
 - Aquatic Toxicity ⁶⁸³
 - Sediment Toxicity
 - Terrestrial Toxicity ⁵
- > Human Health Hazards

Hide positions without QSARs

Available QSARs

- Daphnia magna 48h EC50 - Danish QSAR DB Leadscope model
- Daphnia magna 48h EC50 - Danish QSAR DB SciQSAR model
- Daphnia magna 48h EC50 - Danish QSAR DB battery model
- ECOSAR: ALGAE 72 h EC50 Thiotetrazoles**
- ECOSAR: ALGAE 96 h EC50 Growth Carbonyl Ureas
- ECOSAR: ALGAE 96 h EC50 Growth Imides
- ECOSAR: ALGAE 96 h EC50 Growth Thiophthalimides

Selected QSARs

- Daphnia magna 48h EC50 - Danish QSAR DB Leadscope model
- ECOSAR: ALGAE 72 h EC50 Thiotetrazoles

Executing workflows and QSARs

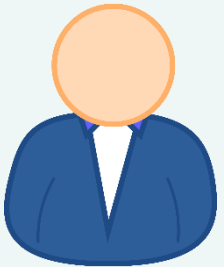
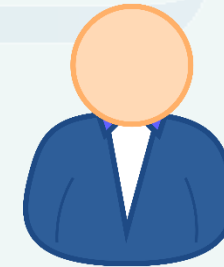
Toolbox Web Client: Improvements

- Input structures with a 2D editor
- Selecting multiple chemicals from a search result
- Improved displaying of data points
- Richer explain service
- Better export

Toolbox Web Client: Deployment scenarios



Connecting to your local Toolbox



Using a shared Toolbox server



Toolbox Web Client: Demo

Launching the WebClient

Overview of the available features

Running a chemical through the workflow

Explaining results

Exporting the matrix

The screenshot displays the QSAR Toolbox web client interface. On the left is a navigation menu with options: INPUT, CALCULATE PARAMETERS, APPLY PROFILING, COLLECT DATA (with sub-options: All data, Specific data), FIND ANALOGUES, RUN WORKFLOWS, RUN QSARs, EXPORT, and a red button for Search IUCLID databases. The main area shows two chemical structures: hexanal (left) and butanal (right). Below them is a table of properties for both substances.

Type to filter...		
Structure info		
CAS #	66-25-1	123-72-8
EC Number	200-624-5	204-646-6
Chemical Name(s)	1-hexanal aldehyde C-6 hexaldehyde hexan-1-ol Hexanal Hexylaldehyde n-Capronaldehyde	Butanal Butyraldehyde BUTYRALDEHYDE, N- isobutyraldehyde n-butanal n-butyraldehyde
Substance Type	Mono Constituent	Mono Constituent
SMILES	CCCCC=O	CCCC=O
Parameters		
Physical Chemical Properties		
Boiling point		
Boiling point	M: 131 °C	M: 74.8 °C
Chemical reactivity		
GSH RCSO	M: Not reactive at saturation	M: Not reactive at saturation
Melting / freezing point		
Melting point	M: -56 °C	M: -99 °C
Partition Coefficient:		
N-Octanol/Air		
Log Koa	M: 4.41	M: 3.39

v. 2.0.2080a

Toolbox Web Client: Future developments

- Scalability improvements (for shared use)
- Integrating metabolism
- Implementing reporting standards