OECD QSAR TOOLBOX v.4.5

ADVANCED AGENDA

I. Important functionalities

1. Alert performance (AP)

AP informs the user on whether the identified alert(s) in the target substance or its metabolites is linked to consistent effects for the endpoint of interest for other substances triggering the same alert and for which experimental data are available. In this respect, calculation of alert performance shows the predictivity of a given alert to the selected endpoint.

AP could be of help in different cases, such as: 1) identification of highly predictable alerts that could be assumed as a SAR; 2) identification of conservative alerts; 3) multiple mechanisms in parent; 4) multiple mechanisms after metabolism; 5) adjusting alert boundaries

2. Metabolic information in Toolbox: Scenarios for using metabolism

Observed and simulated metabolism information could be obtained in Toolbox. The metabolic simulators available in Toolbox can predict the generation of possible metabolites, which allows their further analysis with respect to mechanisms, data availability and use for read-across purposes.

The metabolic information in Toolbox could have broader use in: 1) predicting endpoints when no alert is found in the target neither in its metabolites: using metabolism for refining the category (in the subcategorization); 2) searching analogues having the same metabolic pattern of activation; 3) searching analogues having specific metabolite; 4) selection of active metabolite for read across, etc.

3. Category consistency

Category consistency (CC) automatically collects and displays information key to establishing physicochemical, structural and mechanistic similarities, as well as any experimental data associated with the endpoint under consideration. In addition, application of the CC functionality automatically create various tables and graphs, based on the collected information, that could be used in the reports later on. This allows justification of different aspects of similarity between the target and analogues to be done.

4. Read-Across Assessment Framework (RAAF) – implementation in Toolbox

RAAF represents a framework for a consistent and structured assessment of grouping and read across approaches under REACH. All different scenarios for read-across predictions and the relevant assessment elements, described in the RAAF could be automatically included in the

Toolbox reports allowing easier evaluation on the scientifically validity of the predictions by the assessors.

5. **Predicting higher tier endpoints (HTE)**

   What we can use from Toolbox and how we could make a prediction for HTE, i.e. endpoints with not well defined toxicity mechanisms such as repeated dose toxicity, reproductive and developmental toxicity. Standard read-across procedure based on similarity between the chemicals and analysis on the available metadata information could be demonstrated.

6. **Applying specific searches**

   QSAR Toolbox has various searching capabilities regarding identification of specific experimental data and/or structural features of parents/metabolites, that could be applied to the regular Toolbox or IUCLID databases. This include searching by a custom profiler for screening purposes; 2) Customized searches for specific chemicals/data; 3) Composition search in IUCLID databases.

7. **Import/export of data**

   Custom data (including IUCLID data) could be imported in Toolbox. Different type of data could be exported from Toolbox to various file formats (including direct data export to IUCLID)

8. **(Q)SAR models in QSAR Toolbox**

   QSAR Toolbox includes a library of different external (Q)SAR models that could be used to predict chemical(s). Models from docked software could be also used in the Toolbox environment (such as TIMES and CATALOGIC models)

9. **Toolbox Repository**

   Public platform for digital distribution of Toolbox components. Any user is able to upload their module or to download modules of interest, developed by other users. Currently, different (Q)SAR models (such as OPERA, VEGA, Kate models), profiling schemes (such as ADME, PBT profilers, etc.) and extensions (e.g. ECHA unlocking plugin) are available on the Repository and could be used in Toolbox after download.

10. **Building and usage of custom calculators**

    Calculators are methods for extraction of experimental or predicted data for the 2D/3D properties of the chemicals. They are also used for data gap filling purposes. By building of custom

calculators one could use their available experimental data as a descriptor in data gap filling stage.

11. Workflow editor

New editor in Toolbox allowing implementation of user-defined decision schemes that could be used for screening or prediction purposes. The Workflow editor (WE) is used to transfer the logic of the previously available automated and standardized workflows from script to understandable and traceable schemes.

Several workflows are available for two main endpoints – skin sensitization and aquatic toxicity. They could be used to make a read-across prediction for a single target or for a chemical list. These workflows are disseminated with the Toolbox installation.

The WE is used to build an automated workflow for predicting acute oral toxicity (AOT AW). The AOT AW includes several scenarios depending on the availability of alert(s) identified in the target or as a result of abiotic or biotic transformations. The AOT AW is in the private domain and it is not disseminated with the official Toolbox installation.

12. Handling of mixtures

Two methodologies for estimating toxicity of set of chemicals acting by the same or different mechanism/mode of action could be applied.

13. Endpoint vs. endpoint correlations

Functionality allowing to analyse the correlation between different endpoints based on available experimental data (e.g. correlation between in vivo LLNA, EC3 vs. in vitro KeratinoSens, EC3)

II. New developments & improvements

1. IUCLID data search

Possibility to search for experimental data in IUCLID databases using the Toolbox web version.

2. Harmonization of data

The harmonization aims to define rules for mapping between the information coming from the different Toolbox databases and the relevant OECD harmonized templates (e.g. "TG 301C" and "OECD Test guideline 301C"). The harmonization for several endpoints (biodegradation, genetic toxicity, aquatic toxicity to fish, acute oral toxicity) is currently ongoing.

3. **Improved Toolbox reports**

The Toolbox reports will be modified in order to be more easily interpretable and to include all of the needed information allowing reproducibility

4. **Combined use of QSAR Toolbox and OASIS software. New modelling concepts for predicting HTE**

New modelling concept has been developed for the cases when the standard read-across procedure cannot be applied (i.e. there are no structurally similar analogues). The new concept is based on the metabolic relationship between the target (considered as a parent) and source chemical (being a metabolite of the target chemical). Based on that, the toxicity of the parent chemical could be assessed qualitatively or quantitatively. For the latter a special algorithm for estimation of the dose of the parent chemical needed to produce toxic metabolite is also developed.