QSAR APPLICATION TOOLBOX, v 4.1
ADVANCED PRACTICAL TRAINING WORKSHOP

BARCELONA, SPAIN
22-24 November 2017
AGENDA

Wednesday, 22 November 2017 (09:00 – 17:00)

09:00-09:15 Registration. Welcome and Introductions/Announcements.

09:15-10:00 OECD QSAR Toolbox – Refreshing basic functionalities

10:00-11:00 **Example 1. Predicting Acute aquatic toxicity** (CAS 95-64-7)

- Using external profile for (non)crowded anilines
- Filtering by QA and test conditions (*Poecilia reticulata, Pimephales promelas*)
- Demonstrating the Model domain
- Using other (external) models for weights of evidence (ECOSAR models)
- Saving QSAR (regression) models
- Reporting prediction results

11:00-11:30 Coffee Break

11:30-12:00 **Parallel running – Acute aquatic toxicity** (CAS 95-64-7)

12:00-13:00 **Example 2. Predicting Genotoxicity and Carcinogenicity** (CAS 95-64-7)

Enhanced functionalities of QSAR Toolbox

- AMES Mutagenicity (-S9, +S9)
- Chromosomal aberration - (Mammalian cell gene mutation assays; In vitro Chinese Hamster) – negative (-S9); positive (+S9). Application of metabolism for improving analogue similarity (the other two approaches of application of metabolism will be shown further on – Metabolism section)
- Carcinogenicity – profiling with accounting for metabolism (DNA + Liver) – maximum values used; atom type (halogenated derivatives) –no analogues
- Using external models (TIMES_AMES) for collecting weights of evidence

*Not implemented yet

Save categorical models as:

- SAR
- Category (domain) in existing profile
- Use of the new category for screening purposes

13:00-14:15 Lunch

14:15-15:00 **Parallel running – Genotoxicity and Carcinogenicity** (CAS 95-64-7)

15:00-15:30 **Example 3. Predicting Repeated Dose Toxicity** (CAS 95-64-7 and/or 108-69-0). Defining endpoint (Rat, Oral (Gavage), Whole body, Total, LOEL)

Example 4. Predicting developmental and reproductive toxicity (DART model of P&G) (330-54-1)

Deriving multiparametric QSARs

Import/export of QSAR (regression) models *

Structural similarity - describing the options

Scale conversion – application for combined use of data obtained by different assays

Manual building of custom profile:

- Crowded anilines - Application for subcategorization (to be presented before running CAS 95-64-7)
- Deactivated α,β unsaturated aldehydes
- PBT profiling scheme - demo
- Filtering inventories by SMART libraries

Example 5. Predicting GHS classification (1A and1B) for skin sensitization (CAS# 123-31-9, 111-40-0, 584-84-9, 51-78-5)

15:30-16:00 Coffee Break

16:00-17:00 **Import/export of data** (Vertical and Horizontal layouts) – building proprietary databases

Export of Toolbox predictions to IUCLID6 through WebServices

Import of data from IUCLID6 to Toolbox through WebServices

*Not implemented yet

Docking external (Q)SAR models to Toolbox:

- Docking of CATALOGIC and TIMES to Toolbox

Example 6. Examples of joint use of external models and Toolbox: Limonene (CAS 5989-27-5, SMILES: CC(=C)C1CCC(C)=CC1)

  - BOD – comparison of results obtained from TB and CATALOGIC
  - Skin sensitization - comparison of results obtained from TB and TIMES

Using External (Q)SAR models in Toolbox:

Example 7. Predicting explosive properties – input by smiles

(O=N(=O)C(CC=CCC(N(=O)=O)(N(=O)=O)N(=O)=O)(N(=O)=O)N(=O)=O)

Example 8. Predicting Photoinduced Toxicity (*D.magna*) (anthracene CAS 120-12-7 and phenanthrene CAS 85-01-8)

Example 9. Predicting 3T3 RNU (if apply need time to calculate 3D)

Example 10. Predicting DART (model of P&G) (CAS 330-54-1)

ECOSAR models in Toolbox

Query Tool functionality. Examples by search for:

- Chemicals which are Ames positive, but with negative Carcinogenicity data
- Chemicals which are Ames Negative, Carcinogenicity positive and DART positive
- Biodegradable and bioaccumulative chemicals
- Non-bioaccumulative (<2.0) and lipophilic (logKow>4 or logKow Exp >4.00)
- Mutagenic chemicals which are not skin sensitizers
- Aldehydes with LC50≤1mg/L
- Extremely reactive chemicals to GHS (RC_{50}<0,099mmol/L) and low acute aquatic toxicity (LC50>10mg/L)

Endpoint vs. endpoint correlations. Examples:

- Acute toxicity vs Reactivity *
- Chronic toxicity vs Reactivity *

*Not implemented yet

- AOT vs Acute aquatic tox
- RDT HESS vs AOT
- Correlations between ToxCast bioactivation data
- AMES vs Chromosomal aberration
- LLNA vs GPMT (use GHS scale)
- LLNA vs Keratino (moderate, high and very high Kera are predictive)
- LLNA vs Dendric
- LLNA vs DPRA
- SS (LLNA) vs AMES (+S9)

17:00 Adjourn

Thursday, 23 November 2017 (09:00 – 17:00)

09:00-09:30 Workflow for category evaluation associated with chemical submissions in Europe

09:30-11:00 Evaluating category consistency of:

- Aldehydes (load file from "Examples" folder)
- Acrylates/methacrylates (load file from "Examples" folder)

11:00-11:30 Coffee Break

11:30-13:00 Endpoint specificity of category consistency.

Example 11. Predicting Acute aquatic toxicity, AMES Mutagenicity and Skin sensitization (CAS 42978-66-5)

Example 12. Predicting Acute aquatic toxicity, AMES Mutagenicity and Skin sensitization (CAS 15625-89-5)

13:00-14:15 Lunch

14:15-15:30 **General use of Metabolism**

Part I: Use of metabolism for identifying analogues

Categorization accounting for metabolisms

Example 13. Predicting Skin sensitization potency – manual and AW/SW for SS.

*Not implemented yet

- CAS 97-53-0 (abiotic activation)
- CAS 56-18-8 (skin biotic activation)
- CAS 28069-72-9 (abiotic activation – AW for SS: predicted Negative due to one most similar analogue)
- 120-47-8 (GPMT) – no activation

Example 14. Predicting chromosomal aberation

- Chromosomal aberration (95647) - C- Nitroso, -, NHOH

Selecting analogues by applying specific criteria for parent and metabolites:

- Identification of formaldehyde releasers related to skin sensitization (CAS 97530)
- Identification of analogues for which the parent is not active (not having alert) but cause skin sensitization as a result of abiotic activation to Quinones (CAS 97530)
- Identification of analogues for which the parent is not active (not having alert) but could cause skin sensitization due to abiotically activation to Hydroperoxides (CAS 138-86-3)

Part II: **Selection of active metabolite**

Example 15. Predicting:

- AMES + S9 (CAS 94-59-7 Safrole)
- Skin sensitization (CAS 97530)
- Chromosomal aberration (95647) – C- Nitroso, NHOH. The method is not applicable (no parents available with these functionalities).

Part III: Subcategorization by accounting for metabolic activation

Example 16. Predicting Skin sensitization

- CAS 97-53-0
- CAS 123-30-8

Handling of Mixtures

CCCCO.CC(=O)c1ccc(Cl)c(Cl)c1Cl.O=C(c1ccccc1)c1ccccc1

*Not implemented yet

- Define quantities for each components (Family- Mass; Unit - mg) as follows:
  - CCCCO – 100 mg
  - CC(=O)c1ccc(Cl)c(Cl)c1Cl – 1 mg
  - O=C(c1ccccc1)c1ccccc1 – 10 mg
- Predicting Acute aquatic toxicity
- Predicting Skin sensitization

15:30-16:00 Coffee Break

16:00-17:00 **Handling of tautomers (with and without accounting for tautomerism for each example)**

Example 17. Predicting Skin sensitization (CAS 577-71-9, CAS 99-56-9)

Example 18. Predicting Ames mutagenicity (CAS 621-31-8 or 120-37-6)

Example 19. Predicting Acute toxicity (CAS 65-45-2, CAS 89-62-3)

AOPs and their implementation in Toolbox – Examples (CAS 97-53-0, CAS 553-97-9, CAS 106-50-3)

17:00 Adjourn

Friday, 24 November 2017 (09:00 – 17:00)

09:00-11:00 Case Studies submitted by participants

11:00-11:30 Coffee Break

11:30-13:00 Case Studies (continued)

13:00-14:15 Lunch

14:15-15:15 Case Studies (continued)

15:15-15:45 Coffee Break

15:45-16:45 Case Studies (continued)

16:45-17:00 Wrap-up Discussion

17:00 Presentation of Certificates and Adjourn

*Not implemented yet