QSAR APPLICATION TOOLBOX, v 4.4.1
ADVANCED PRACTICAL TRAINING WORKSHOP

BARCELONA, SPAIN
AGENDA

Day 3 (09:00 – 17:00)

Two coffee breaks: 11:00-11:30; 15:30-16:00

Lunch: 13:00-14:15

I. **OECD QSAR Toolbox** – Summary of the basic functionalities

II. **Building knowledge platform and usage – Part I**

a. Building custom profiler for subcategorization: (Non)crowded anilines

Examples:

1) (Non)crowded anilines
   - Predicting Acute aquatic toxicity (CAS # 95-64-7)
   - Predicting Ames mutagenicity – S9 (CAS # 95-64-7)

III. **(Q)SAR models in QSAR Toolbox – Part I**

a. ECOSAR models included in TB

b. Danish EPA models included in TB

Examples:

1) Predicting Acute aquatic toxicity by ECOSAR models (CAS # 95-64-7)
2) Predicting Ames mutagenicity by Danish EPA models (CAS # 95-64-7)

IV. **Scenarios for using metabolism**

a. Using metabolism for refining the category (in the subcategorization)

b. Searching analogues having the same metabolic pattern

c. Searching analogues having specific metabolite

d. Selection of active metabolite for read across

e. Combination of queries for the parent and metabolites

Examples:

1) Refining category by using metabolism AMES +S9 - CAS # 95-64-7
2) Identification of p-benzoquinone releasers (MNT, CAS # 150-76-5)
3) Selection of active metabolite - AMES +S9 CAS # 94-59-7 (Safrole)
4) Combination of queries: SS, CAS 97-53-0

V. Alert performance and its application – Part II

a. Multiple mechanisms after metabolism

b. Adjusting alert boundaries

Examples:

1) Multiple mechanisms after metabolism - SS - CAS # 56-18-8
2) Adjusting alert boundaries – (only information)

VI. Predicting endpoints when no alert is found in the target neither in its metabolites –

CAS # 120-47-8 (GPMT) – no activation

VII. Category consistency

a. Endpoint specificity of category consistency. (acrylates/methacrylates)

b. Implementation of category consistency in Toolbox SS - CAS # 56-18-8

VIII. Building knowledge platform and usage – Part II

a. Building custom profiler for screening purposes: Formaldehyde releasers

Example:

- SS – abiotic activation - CAS # 97-53-0
- MNT – in vivo rat liver – CAS 150-76-5

Day 4 (09:00 – 17:00)

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I. Predicting higher tier endpoints

a. Repeated dose toxicity

b. Reproductive toxicity

c. Developmental toxicity

Examples:

1) Predicting Repeated Dose Toxicity (RDT, NOAEL, rat):
    i. CAS 60-12-8 – strict OFG,NH
    ii. CAS 140-26-1 – RA using acidic hydrolysis product
2) Predicting reproductive toxicity
    i. NOAEL, rat: CAS 1120-24-7; Apply GL 422
        - Overall reproductive toxicity and gross pathology
    ii. ERBA+S9: CAS 122-97-4
        - ERBA data for in vitro rat metabolites
3) Predicting developmental toxicity
    i. CAS 26402-26-6 (CAS 85-68-7)- Metabolic activation to be simulated:
        - Structural similarity – failure to make straightforward prediction
        - Searching active metabolites of the parent - in vivo rat metabolism simulator and DART profiling
            - with experimental data or
            - RA of active metabolite
        - Category definition accounting for metabolism
            - Searching analogues having the same reactive pattern - failure
            - Searching analogues having the same reactive metabolite – exact match Show AP; explain profiling results

II. (Q)SAR models in QSAR Toolbox – Part II

a. Other QSAR models that could be included in TB: VEGA and KATE models

b. (Q)SAR models docked to Toolbox

c. Custom (Q)SAR models

Examples:

1) Predicting bioaccumulation by VEGA models – CAS 120-83-2
2) Predicting aquatic toxicity by KATE models – CAS 120-83-2
3) Predicting human health and environment endpoints

- Predicting Ames mutagenicity by the TIMES system (CAS # 94-59-7, Safrole)
- Predicting BOD by the CATALOGIC system (CAS # 5989-27-5, Limonene)

4) (Q)SAR editor - create a new model

- With equation

Example:

Endpoint: Ecotoxicological Information / Aquatic Toxicity

Growth/ 48 h / Tetrahymena pyriformis / IGC50

Units: Molar concentration; mol/L, log(1/Endpoint)

Model equation: 2.09+0.555*logKow

Training set and Validation set: available in the Example folder

Domain – define:

- reference query and take "Aldehyde (acute toxicity)" from *US EPA New Chemical Categories* profiler
- parametric query: logKow (0.3;5)

- with web-service link

http://qsardb.org/repository/service/predictor/10967/104/**models/**rf**?<smi>**

Reference link**: http://qsardb.org/repository/service/predictor/10967/104**

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

a. Scenario 1 ((Bio)transformation to common compound(s))

b. Scenario 2 (Different compounds having the same type of effect(s))

Examples:

1) Scenario 1

- Human health
  - One of the transformation products used as a source – RDT, CAS # 140-26-1
  - The target and source chemicals have common metabolite – MNT, CAS # 150-76-5
- Environmental
  - NOEC, 21d, Reproduction, D. magna – Scenario 1 (CAS 2428-04-8)

2) Scenario 2

- The target and source chemicals have the same PBA – SS, CAS # 56-18-8

IV. Import/export of data – building proprietary databases; transferring data to / from IUCLID 6.3

V. Query Tool functionality – strategic search for data / chemicals

- 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

VI. Endpoint vs. endpoint correlations

b. Acute toxicity vs Reactivity
c. AOT vs Acute aquatic tox
d. RDT HESS vs AOT
e. Correlations between ToxCast bioactivation data
f. AMES vs Chromosomal aberration
g. LLNA vs GPMT (use GHS scale)
h. LLNA vs Keratino (moderate, high and very high Kera are predictive)

i. LLNA vs Dendric
j. LLNA vs DPRA
k. SS (LLNA) vs AMES (+S9)

VII. Handling of mixtures

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

- 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
  -

VIII. AOPs and their implementation in Toolbox (CAS # 97-53-0, CAS # 553-97-9, CAS # 106-50-3)

<u>Day 5 (09:00 – 17:00)</u>

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Case studies