

QSAR APPLICATION TOOLBOX, v 4.4.1

ADVANCED VIRTUAL TRAINING WORKSHOP

AGENDA

Day 1

Two breaks – 15` every hour and half

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**Day 2**

Two breaks – 15` every hour and half

I. (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: $2.09+0.555*\log Kow$

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>

II. 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

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

Day 3

Two breaks – 15` every hour and half

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. 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:
 - CCCCCO – 100 mg
 - CC(=O)c1ccc(Cl)c(Cl)c1Cl – 1 mg
 - O=C(c1cccc1)c1cccc1 – 10 mg

Day 4

Two breaks – 15` every hour and half

I. Category consistency

- a. Endpoint specificity of category consistency. (acrylates/methacrylates)
- b. Implementation of category consistency in Toolbox SS - CAS # 56-18-8

II. 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

III. 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 ($\log K_{ow} > 4$ or $\log K_{ow} \text{ Exp} > 4.00$)
- Mutagenic chemicals which are not skin sensitizers
- Aldehydes with $LC50 \leq 1 \text{ mg/L}$

IV. Endpoint vs. endpoint correlations

- Acute toxicity vs Reactivity
- 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)

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