Exemplification of the integration of tools within REACH: the CADASTER project

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CADASTER: Exemplification of tools within REACH

CADASTER: CAse studies on the Development and Application of *in-Silico* Techniques for Environmental hazard and Risk assessment

PBDE: "The PCB's of the future"

Classification of PFOS-compounds in 22 categories according to OECD
REACH Registration, Evaluation, Authorisation and Restriction of Chemicals

REACH requires demonstration of safe manufacture and use of chemicals

REACH based on precautionary principle, aims at achieving proper balance between social, economic and environmental objectives

REACH aims to optimise the use of scarce and scattered info on substances

REACH aims to minimise animal testing by optimal use of info on "related" compounds
Intelligent Testing Strategies (ITS)

Read Across

(Q)SARs

In-vitro

Endpoint information

Exposure Scenarios (Annex VII/VIII)

Existing information

? 

TESTING
Goals:

● Exemplify the integration of information, models, strategies for safety-, hazard-, risk assessment for large numbers of substances
● Carry out “real” risk assessment for large numbers of substances according to the basic philosophy of REACH: < costs, animal testing, time
● Exemplify how to increase non-testing information whilst quantifying and reducing uncertainty
Aim:
Provide full environmental hazard and risk assessment according to the REACH philosophy for chemicals belonging to 4 classes of emerging chemicals:

● 1 – Polybrominated diphenylethers (PBDE), hydrophobic chemicals that pose a threat to man and the environment.

● 2 - Perfluoroalkylated substances and their transformation products, like perfluoroalkylated sulfonamides, alkanoic acids, sulfonates. Persistent hydrophilic compounds that may be toxic for man and environment.

● 3 – Substituted musks/fragrances; a heterogenic group of chemicals of varying composition like substituted benzophenones, polycyclic musks, terpene derivatives. Common emission pattern in the environment.

● 4 - Triazoles/benzotriazoles: increasingly used as pesticides and anti-corrosives.
Outcome:
DSS – regularly updated for new compound classes:
- New testing strategies
- New testing data
- New models
- Actual integrated evaluations, including uncertainty and variability

- On-line and stand-alone tool
Activities

1: Collection of data and models
- Experimental data intrinsic hazards – Screening Initial Data Set Dossier (SIDS)
- Models – Screening Initial Data Set Dossier (SIDS)
- Generation new data essential for validation and proper hazard/risk assessment
- Database data/models: dissemination purposes
Activities

2: Development/validation QSAR models
- Evaluate performance
- Similarity analysis and multivariate ranking methods for identification of priority chemicals to orient the experimental testing
- Develop new QSARs where gaps are identified due to lack of existing models or due to models of insufficient quality.
- Documentation of the performance of the (final) models selected and developed.
Activities

3: Integration of QSARs within hazard and risk assessment

- Integration in probabilistic risk assessment framework: characterize variability/uncertainty, sensitivity analyses, modeling of variability with regard to application in SSDs
- Evaluate ECETOC TRA screening RA tool
- Evaluate methods and decision points for establishing scientific validity and applicability domains for QSAR models
- Explore possibilities for economic valuation of substitution of chemicals from within chemical classes
4: **Outreach**: website, newsletters/ workshops, stand-alone tools for dissemination of project results

- Development of on-line, stand-alone DSS: develop, publish, use QSAR/QSPR models for REACH

- Integration of the developed models with the QSAR Application Toolbox developed by OECD: establish the compatibility of the models with the (Q)SAR Model Reporting Format (QMRF) format

- Provision of a sustainable dissemination of project results by the WWW and as stand-alone tools

- Communication including newsletters and workshop(s).
Some findings

- Lack of sufficient data for relevant endpoints
- Lack of models for relevant endpoints and relevant chemical classes
- Difficult to obtain data from industry

- > 7500 data entries relevant for RA – 4 classes
- Overview of suited (Q)SAR models available
- Identified: need for new/improved models
Toxicity testing of PerFluorinated Compounds

Strategy:
1 – Experimental design: PCA + read across toxicity data other (rodent) species
2 – Selection of ideal set of test compounds
3 – Acquiring test compounds
4 – Design non-ideal set of test compounds
5 – Toxicity assessment
6 – Modelling
Work of University of Insubria

- Inhalation study: 4 descriptors based MLR model
  - Hydrophobicity ($M\log P$) → negative
  - Electronegativity ($J\text{hetv}, X3v$ and $\text{MATS1e}$) → positive

- Oral study: 4 descriptors based MLR model
  - Fingerprint descriptors representing frequency of atom pairs like C-C, C-F and C-O are prominent

- 376 extra PFCs predicted including PFCs listed in ECHA

- Prediction and prioritization of toxic PFCs based on rodents toxicity
CADASTER

- PFCs
- PFCs with benzimidazole ring

Graph with data points categorized by different exposure routes and concentrations.
PCA DRAGON descriptors
Extended set of compounds

- Butanoic acid, heptafluoro-, ethyl ester
- Methacrylic acid, 2,2,3,3,4,4,4-heptafluorobutyl ester
- 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanethiol
- 1H,1H,2H,3H,3H-Perfluorononane-1,2-diol; 97%
- 1H,1H,2H,2H-Perfluorooctyl isobutyrate
- 2,2,3,3,4,4,5,5,6,6,7,7-Dodecafluoro-1,8-octanediol
Extended set of compounds

Amine
Aquatic Testing

<table>
<thead>
<tr>
<th>Organism</th>
<th>End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lettuce</td>
<td>root length elongation</td>
</tr>
<tr>
<td>Algae</td>
<td>Photosynthesis inhibition</td>
</tr>
<tr>
<td>Daphnids</td>
<td>Survival</td>
</tr>
<tr>
<td>Zebra fish</td>
<td>Early life stage testing (embryo)</td>
</tr>
</tbody>
</table>
Results - acids

Log EC50, lettuce = 
\[-0.170 \times nC + 1.197\]

\(n = 5, R^2 = 0.853, p = 0.0252\)

Log EC50, algae = 
\[-0.156 \times nC + 1.313\]

\(n = 4, R^2 = 0.988, p = 0.006\)
Interspecies extrapolation read across daphnids

**Daphnia magna**

Log EC50, 24h = $0.127 \times nC + 0.646$

$n = 5, R^2 = 0.986, p = 7.090 \times 10^{-4}$

Log EC50, 48h = $0.131 \times nC + 0.615$

$n = 6, R^2 = 0.971, p = 3.265 \times 10^{-4}$

**Chydorus sphaericus**

Log EC50, 24h = $0.214 \times nC + 1.013$

$n = 7, R^2 = 0.972, p < 0.0001$

Log EC50, 48h = $0.221 \times nC + 0.876$

$n = 7, R^2 = 0.925, p = 5.394 \times 10^{-4}$

**24h toxicity:**

Log EC50, C. sphaericus = $1.560 \times \log$ EC50, D. magna $- 0.113$

$n = 5, R^2 = 0.888, p = 0.016$

**For 48-h toxicity:**

Log EC50, C. sphaericus = $1.494 \times \log$ EC50, D. magna $- 0.277$

$n = 6, R^2 = 0.846, p = 0.009$
CADASTER posters at SETAC 2011

**MO-305 (PE01)**
Exploring the QSARs for OH Tropospheric Degradation of VOCs using freely available online descriptors.

**MO-306 (PE01)**
On the agreement of external validation parameters for linear regression QSAR models

**TU-112 (ET01)**
Stepwise D-Optimal design based on latent variables

**TU-337 (RA11)**
Study on the toxicity of perfluorinated compounds to aquatic organisms

**TU-335 (RA11)**
A QSAR-based compound prioritization for lab-testing for chemical safety assessment

**TU-342 (RA11)**
MOPAC@home – an online database for small organic compounds

**TU-346 (RA11)**
QSAR and QSPR models for emerging pollutants: WP3 activities within the FP7 European Project CADASTER

**TU-347 (RA11)**
Physico-chemical property prediction of emerging pollutants: PFC and (B)TAZ for environmental distribution.

**TU-348 (RA11)**
QSAR prediction of aquatic and mammalian toxicity of triazoles and benzo-triazoles