HelmholtzZentrum münchen
German Research Center for Environmental Health

Case studies on the Development and Application of *in silico* Techniques for Environmental hazard and Risk assessment (CADASTER)

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Motivation

Some 30 000 existing substances are to be assessed through the REACH process. REACH advocate ***the use of non-animal testing methods***.

However, so far the use of these methods in the European regulatory context is quite limited and fragmented. Reasons include the lack of distinct application criteria and guidance, and the fact that quality and uncertainty of models developed in the QSPR field, including validation and applicability domain of models, frequently is not addressed rigorously and remains a difficult issue. The internationally agreed application criteria and guidance, issued by Organisation for Economic Co-operation and Development (OECD) are aimed to improve this situation.

Goal

Our project will exemplify the integration of information, models and strategies for carrying out safety-, hazard- and risk assessments for large numbers of substances to the new categories of risk assessors within REACH.

We will deliver real risk estimates according to the basic REACH philosophy of minimizing animal testing, time and costs. CADASTER will show how to increase the use of non-testing information for regulatory decision whilst meeting the main challenge of quantifying and reducing the level of uncertainty of predictions.

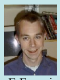
Partners


W Peijnenburg (Coordinator)


M Huijbregts


M Durjava


P Gramatica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Universiteit Nijmegen één in weten

Public Health Institute Maribor

University of Insubria

IVL Swedish Environmental Research Institute

Högskolan Kalmar

HelmholtzZentrum münchen Deutsches Forschungszentrum für Gesundheit und Umwelt

IdEA consult

Mike Comber Consulting (MCC)

WP Collection of data and models

1. Collection of existing experimental data on the most common regulatory endpoints considered in the Screening Initial Data Set Dossier (SIDS) for the four classes of chemicals selected.
2. Collection of existing (Q)SARs for the endpoints considered in the SIDS.
3. Generation of new data on endpoints and chemicals for which, insufficient data are available.
4. Development of a database on experimental data.

WP Development and validation of QSAR models

1. Evaluation of the performance of existing QSARs for the chemical classes studied.
2. Similarity analysis and multivariate ranking methods for identification of priority chemicals in the selected classes to orient the experimental tests in WP2.
3. Development of new QSARs where gaps are identified due to lack of existing models or due to models of insufficient quality.
4. Documentation of the performance of the (final) models selected and developed.

WP Integration of QSARs within hazard and risk assessment

1. Integration of QSAR models into a probabilistic risk assessment framework.
2. Evaluation of the ECETOC TRA risk assessment tool.
3. Evaluation of methods and decision points for the establishment of scientific validity and applicability domains for QSAR models.
4. Exploring the possibilities for economic valuation of substitution of chemicals from within chemical classes.
5. Policy and management: recommendations on a viable management strategy for optimized testing and *in silico* modeling of hazardous organic substances.

WP Development of website and stand-alone tools for dissemination of project results

1. Development of on-line and stand-alone Decision Support System (DSS) for development, publishing and use of QSAR/QSPR models for REACH.
2. Integration of the developed models with the QSAR Application Toolbox developed by the OECD and establishing the compatibility of the models with the (Q)SAR Model Reporting Format (QMRF) format.
3. Provision of a sustainable dissemination of project results by the WWW and as stand-alone tools.

Main collaborations that we are looking for

- Data on experimental toxicity for any of the analyzed classes of molecules.
- Data for physico-chemical properties and chemical reactivities
- Integration of the models within the OECD QSAR tool box.
- Collaboration with the USA EPA/FDA, OpenTox (EU)

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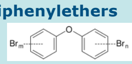
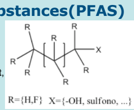
Polybrominated diphenylethers



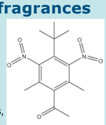
Flame retardants used in plastics, foams, fabrics, etc. The PBDEs persist in the environment and accumulate in living organisms, as well as toxicological testing. These chemicals may cause liver toxicity, thyroid toxicity, and neuro-developmental toxicity. The traces of several PBDEs were found in human breast milk, fish, aquatic birds, and elsewhere in the environment. Particular congeners, tetra- to hexabrominated diphenyl ethers, are the forms most frequently detected in wildlife and humans.

Perfluoroalkylate substances(PFAS)



and their transformation products, like perfluoroalkylated sulfonamides, alkanoic acids, sulfonates. Fluorinated compounds are typically a class of persistent, relatively hydrophilic compounds that may be toxic for man and environment. The most important route is emission due to wear of PFAS treated tissues (carpet, textile, leather) as well as from fluorochemical production sites. The most important bioaccumulation in biota are blood and liver. The half-life time can be as long as 10 years and they are highly bioaccumulative (factor of ca 10^5).

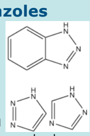
Substituted musks/fragrances



Musk Ketone

A heterogenic group of chemicals of varying composition that are used extensively in detergents, perfumes, shampoos, and other personal care products. Examples include substituted benzophenones, polycyclic musks, terpene derivatives. In view of their typical use pattern, the chemicals have a common emission pattern in the environment.

Triazoles/benzotriazoles



These substances are widely applied as anticorrosives, e.g., in aircraft deicer and anti-icer fluid and in so-called silver protection in dishwasher detergents. Due to their low biodegradability and limited sorption tendency, they are only partly removed in wastewater treatment. The observed environmental occurrences indicate that these molecules are ubiquitous contaminants in the aquatic environment and that they belong to the most abundant individual water pollutants.

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Institute of Bioinformatics & Systems Biology

HELMHOLTZ ASSOCIATION