CADASTER

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

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Collaborative Project

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Workshop on the use of QSARs models in REACH (Deliverable 5.6)

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WP 5: QSPR-THESAURUS: Web site and standalone tools for dissemination of project results

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Task 5.6- Workshop on the use of QSAR models in REACH (Deliverable 5.6)

Summary

The CADASTER workshop (http://www.cadaster.eu/node/116) was organized by the Public Health Institute Maribor (PHI) in Maribor, Slovenia, as a part of the CMPTI conference (http://cmtpi-2011.si) and took place from September 1st to 2nd 2011. The workshop aimed to assist the risk assessors and national chemicals authorities, particular in Eastern European countries, with the use of the QSAR tools for the environmental risks assessments in REACH.

The workshop involved 35 participants, including invited speakers from JRC - Institute for Health & Consumer Protection (Italy), ECHA – Evaluation Unit (Finland), Douglas Connect (Switzerland) and University of North Carolina USA).

On 1 September, there were presentations of CADASTER partners giving an overview of the CADASTER project and the results of the project:

- General philosophy of CADASTER (Willie Peijnenburg RIVM, The Netherlands);
- CADASTER achievements (Mojca Kos Durjava, PHI Maribor, Slovenia).

In addition three invited speakers gave an overview on the FP7 OpenTox project and on different aspects of alternative methods in REACH:

- How OpenTox satisfies REACH requirements (Barry Hardy, Douglas Connect, Switzerland);
- Legislative overview on the use of alternative methods in REACH (Evelin Fabjan, ECHA, Finland);
- Technical information on alternative methods (Andrew Worth, JRC, Italy).

On 2 September, the fourth invited speaker gave an overview about the state of the art on QSARs and CADASTER partners gave presentations about the CADASTER achievements:

- Information about state of the art on QSARs (Alex Tropsha, University of North Carolina, USA);
- CADASTER achievements (Paola Gramatica, University of Insubria, Italy);
- CADASTER results (Tomas Oberg, Linnaeus University, Sweden; Igor Tetko, HMGU, Germany).

In addition, training lessons for on-line tools were given:

- Training lessons for on-line tools that can be used to estimate REACH end-points for chemical compounds and decrease the number of animal tests: Demonstration of the tools developed in CADASTER (Igor Tetko, HMGU, Germany);
- Demonstration of the models available in the OECD QSAR toolbox (Emil Rorije, RIVM, The Netherlands).

The workshop was concluded with a panel discussion:

- Panel Discussion on the use of QSARs in REACH (Willie Peijnenburg, RIVM, The Netherlands).

The subsequent feed-back of the workshop participants on their experiences with the implementation of REACH was of importance for the customization of the tools for the use by the regulatory agencies.

Contents

Introduction

The REACH regulation advocates the use of non-animal testing methods for risk assessment of chemicals, but guidance is needed on how these methods should be used. The procedures include alternative methods such as chemical and biological read-across, *in vitro* results, *in vivo* information on analogues, (Q)SARs and exposure based waiving. The concept of Intelligent Testing Strategies (ITS) for regulatory endpoints has been outlined to facilitate the assessment.

CADASTER aims at providing the practical guidance to integrated environmental risk assessment procedures by carrying out a full environmental hazard and risk assessment for chemicals belonging to four selected compound classes. The following compounds were selected as the chemical classes of choice for CADASTER:

1. Polybrominated diphenylethers (PBDE), typically being a class of hydrophobic chemicals that pose a threat to man and the environment.
2. Perfluoroalkylated substances 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.
3. Substituted musks/fragrances, being a heterogenic group of chemicals of varying composition. 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.
4. Triazoles/benzotriazoles, a class of chemicals that are increasingly used as pesticides and anti-corrosives.

Within CADASTER much attention is given to application of existing QSARs and development of new QSAR models. QSAR models are developed and validated, also externally, according to the OECD principles for the validation of QSAR because the validation of (Q)SAR models is essential for their regulatory use.

The QSAR models and data produced during the project were made publicly available and are accessible to all interested partners and stakeholders. They are available as an on-line and standalone tools (because of the complexity of used descriptors, the calculations are performed on the web site of the project) and there is currently a negotiation with the OECD QSAR Toolbox to incorporate them as part of the toolbox. It will be freely distributed to SMEs and other industrial partners. The support and development of new models is expected to be continued after the end of the project by the eADMET GmbH (http://www.eadmet.com) company.

This report provides an overview of the CADASTER workshop on the use of QSARs in REACH (http://www.cadaster.eu/node/116). The workshop was organized in Maribor, Slovenia by the Public Health Institute Maribor and took place from September 1st to 2nd 2011. The workshop was organized as a part of the CMPTI conference (http://cmtpi-2011.si). The overview of the CADASTER workshop is complemented with four appendices: appendix 1 contains a list of commonly used abbreviations in the

report; appendix 2 contains the programme of workshop; the list of participants is given in appendix 3, whereas appendix 4 contains abstracts of the presentations given during the workshop.

Important points from the workshop discussions

The program of the CADASTER workshop (see Appendix 2: Programme of the CADASTER Workshop) was a combination of plenary sessions to provide a common perspective to all of the attendees and of training lessons for on-line tools that can be used to estimate REACH endpoints for chemical compounds. Bellow the most relevant points from discussions are listed:

- Industry should work together and realize how important it is to share the data.
- At the moment, i.e. in the current phase of notification and administration of chemical substances as required by the REACH legislation with focus on high production volume chemicals, QSARs are not used much in particular for endpoints that may require testing on vertebrate animals. This is despite the one of the major aims of REACH of reduction of animal testing. The key problem is justification of the adaptation of experimentally generated data towards calculated data: the need to show that the calculated data have the same accuracy as experimental data. This issue deals amongst others with the issue of availability of scientifically sound (i.e. mechanistically based), generally accepted (i.e. amongst others reported according to the agreements within OECD with regard to QMRF), and properly validated QSARs.
- More expertise on QSAR development is necessary in judging, using, and proposing QSAR models: in ECHA, in Industry, and in the regulatory community at large.
- ECHA should encourage the evaluators to use alternative methods correctly.
- Information from dossiers is publicly available at ECHA web site.
- The industry is only to a small extent using QSARs for the first evaluation of the toxicity, but not at all for Classification and Labeling.
- QSARs are hardly used by industry for predicting fate and effect properties for high production volume chemicals, despite the fact that using results of QSARs is cheaper, whereas QSARs allow to generate predictions for large numbers of chemicals. This is due to the fact that there is the concern within industry that risk assessors still have doubts on the uncertainties associated with generating QSAR estimated. On the other hand, as the first phase of the risk assessment process within REACH deals only with the chemicals produced and marketed at the highest tonnages, there is no economic restriction for industry to generate new experimental data for virtually all high tonnage chemicals.
- It is expected that in the subsequent stages of REACH (i.e.: the phases dealing with “lower-tonnage” chemicals), the use of alternative methods will strongly increase as the economic advantage of the use of alternative methods will become more evident for these chemicals.
- Developed and published models should be publicly or commercially available. It is not always possible to exactly reproduce the published models due to differences in data preprocessing, aromaticity calculation, differences in software versions, use of different structure

representations, etc. All these details are usually omitted from publications. Ignoring these important details could result in significantly different models. In particular, this problem is relevant to computational models that are developed using 3D descriptors. Optimization of 3D structures is a non-deterministic process and, thus, these models are usually very difficult to reproduce. That is why CADASTER stores also the calculated values for some models, which were provided by the authors. These values as well as information about AD of predictions for them are accessible by users on the Web.

- QSAR models are not generally accepted since to some extent they represent a “black box” and thus the regulators cannot clearly see an interpretation of the model from its equation.
- A complex non-linear model that is accomplished by adequate interpretable explanation could be accepted by the regulators.
- For the success of CADASTER as well as of other EU projects, it would be very important to have an option to export all data from the OECD Toolbox, which is currently absent.
- The predictive toxicology modeling community would benefit from ECHA making submission information available in a more useful form for modeling purposes, e.g., to make it interoperable with OpenTox services and applications.
- It would be of benefit for a number of projects and organizations to collaborate in the development of best practices and guidance for read across and weight of evidence (which can include use of (Q)SAR), e.g., an extension and update of the OECD principles for (Q)SAR.
- Collaboration between health and environment for knowledge exchange, method extension, tool integration and standards and harmonization would provide benefits.

CADASTER workshop Panel Discussion

1. **What are that major barriers for a wider use of alternative and in particular *in silico* methods in REACH?**

   Despite progress in using QSARs for regulatory purposes there are still limitations present due to the limited number of models currently available, lack of experience of using models for regulatory purposes and because of lack of experimental data available for developing new models for particular endpoints.

2. **What is your (industry) experience with the use of *in silico* methods for REACH?**

   If it is uncertain whether regulators will accept a QSAR prediction, then industry will prefer to use a traditional experimental method in order to avoid uncertainty and delay in regulatory approval. The level of uncertainty for industry in achieving regulatory approval is therefore currently lower if traditional methods are chosen rather than QSAR models. There is also currently far less knowledge in industry about QSAR models than about traditional experimental methods.

3. **As a regulator, which criteria will be important for you to accept the *in silico* model results?**

   REACH legislation promotes the use of alternative methods. However, in practice, the use of *in silico* models within REACH by European industry is still very limited. According to REACH regulation (Annex XI) a (Q)SAR is valid if:

   - the model is recognized as scientifically valid;
   - the substance is included in the applicability domain of the model;
   - results are adequate for classification and labeling, for risk assessment or for prioritization of substances;
   - adequate documentation of the methods is provided.

4. **As an industry, will you be willing to share your experimental data for QSAR/QSPR models development for REACH?**

   After the introduction of REACH the sharing of data is much easier, but sharing of data has become a financial issue due to the high costs associated with the generation of experimental data.

5. **What are your recommendations and how can we improve our tools?**

   The challenge for developers is to produce models that are not just scientific but also functional and fit for the purpose within the regulatory context. Any lack of documented information about a model is simply a guaranteed barrier to its acceptance.

6. **When Daphnia (and algae) can also predict fish toxicity this would limit fish testing. Which modes of actions for the 4 groups could result in additional fish toxicity compared to algae and daphnia?**

   For (benzo)triazoles we confirm a good correlation for fish, and daphnia toxicity. The data for daphnia can be used to extrapolate toxicity from daphnia to fish. For other classes (PBDE,

perfluoroalkylated substances, substituted musks/fragrances) we do not have sufficient data on aquatic toxicity to develop a reliable model.

7. **The uncertainty of QSAR results becomes important when they are close to the cut off values of C&L and PBT assessment because of regulatory implications. Because under REACH safe use of chemicals needs to be ensured via risk characterization the regulatory implications on C&L may become less important but not for PBT?**

   The demands for C&L contrast with those for RA in several important respects. There is potential for significantly wider use of QSAR models in the evaluation of chemicals where there is lack of existing data for C&L. In the third regulatory use of QSAR models, for prioritization, the situation appears to be more straightforward. Neither the lower number of endpoints of interest, nor the potential uncertainty of the results, is critical, because the goal is to determine which chemicals require higher scrutiny.

8. **Can the BCF models predict the BCF of reactive chemicals (e.g. hydrolyzing compounds like esters, or protein binders) or readily biodegradable chemicals to potentially decrease the probability for bioaccumulation?**

   The answer to this question was unanimous: “No, this is currently not possible by BCF models as these models do not include modules for reactive compounds or compounds instable in the aquatic or terrestrial environment”.

9. **It seems that there is a lack of environmental data for the four selected CADASTER chemical classes**. **Regarding the (eco)toxicity, most of the CADASTER QSAR models developed are an animal toxicity models. What can be done to connect these two, any suggestion from REACH/ECHA?**

   In addition to what was already done: Compile all the available data are in dossiers published by ECHA.

10. **Regarding proprietary data from industry: Can’t it be used to use models keeping data and model still proprietary to predict the properties? The statistics of the model could be shown to know the model is valid.**

    This is something that is necessary to be considered by the regulator. It is not enough to see just the model and its statistics, but also the transparency of the model, calculation behind the model.

11. **Is there a future for traditional QSAR in regulatory toxicology?**

    QSAR models now and in the future may prove to be an increasingly valuable technology, with a potentially important function for protecting human health and the environment. It is in the interests of all stakeholders that QSAR models are explained openly and used appropriately with care. Future debate needs to clarify the acceptable uncertainty in data from QSAR models across the different regulatory functions.

Future activities

In the autumn of 2012 the final CADASTER workshop will be organized by the Helmholtz Zentrum München in Munich, Germany. The second workshop will provide a tutorial to all interested partners, including industry and SMEs, on how to develop new models for the assessment of REACH-end points (in particular for new scaffolds of compounds for which there are no reliable QSAR models) and how to use the software developed by the project participants. The materials of the workshop will be published in a special issue of a scientific journal (it is not yet decided in which journal the materials will be published). The special issue will summarize the expertise of all CADASTER participants by providing clear guidelines on how to integrate different testing strategies, how to develop models, and how to estimate their applicability domain following a critical analysis of the four case studies considered in the CADASTER grant.

Acknowledgements

We thank the organizer of the CMTPI conference, the National Institute of Chemistry Slovenia and Professor Vracko, who kindly offered the cooperation between the CMTPI conference and the CADASTER workshop.

This report was prepared by Dr. Mojca Kos Durjava, the organizer of the workshop with remarks and contributions of the leader of the CADASTER project Professor Willie Peijnenburg, and WP leaders, namely Professor Paola Gramatica, Professor Tomas Öberg and Dr Igor Tetko.

The organizer would like to thank all of the speakers, who provided a background for the subsequent discussions and all participants who generously contributed their time and effort to the planning and the implementation of the workshop.

Publications

The list of CADASTER publications is regularly updated at the CADASTER website (http://www.cadaster.eu/node/35). Currently, the list is as follows:

Bhhatarai, B.; Gramatica, P. Modelling physico-chemical properties of (benzo)triazoles, and screening for environmental partitioning *Water Research*, **2011**, 45, 1463-1471

Bhhatarai, B.; Gramatica P. Per- and Polyfluoro Toxicity (LC50 Inhalation) Study in Rat and Mouse Using QSAR Modeling *Chem. Res. Toxicol.*, **2010**, 23, 528-539.

Bhhatarai, B.; Gramatica, P. Oral LD50 Toxicity Modeling and Prediction of Per- and Polyfluorinated Chemicals on Rat and Mouse *Molecular Diversity*, **2011**, 15 (2), 467-476

Bhhatarai, B.; Gramatica, P. Prediction of Aqueous Solubility, Vapor Pressure and Critical Micelle Concentration for Aquatic Partitioning of Perfluorinated Chemicals *Environ. Sci. Technol.*, **2011**, 45(19), 8120-8128

Bhhatarai, B.; Teetz, W.; Liu, T.; Öberg, T.; Jeliazkova, N.; Kochev, N; Pukalov, O.; Tetko, I.; Kovarich, S.; Papa, E.; Gramatica, P. CADASTER QSPR Models for Predictions of Melting and Boiling Points of Perfluorinated Chemicals *Molecular Informatics*, **2011**, 30, 189-203

Chirico, N.; Gramatica, P. Real External Predictivity of QSAR Models: How To Evaluate It? Comparison of Different Validation Criteria and Proposal of Using the Concordance Correlation Coefficient *J. Chem. Inf. Model.*, **2011**, 51 (9), pp 2320–233

Iqbal, M.S.; Öberg, T. Description and propagation of uncertainty in input parameters in environmental fate models *Submitted*

Kovarich, S.; Papa, E.; Gramatica, P. QSAR classification models for the prediction of endocrine disrupting activity of brominated flame retardants *J. Hazard. Mater.*, **2011**, 190 (1-3), 106-112

Liu, T.; Nicholls, I.; Öberg, T. Comparison of theoretical and experimental models for characterizing solvent properties using reversed phase liquid chromatography (RPLC) *Analytica Chimica Acta*, **2011**, 702, 37-44

Öberg, T.; Liu, T. Extension of a prediction model to estimate vapor pressures of perfluorinated compounds (PFCs)s *Chemometrics and Intelligent Laboratory Systems*, **2011**, 107, 59-64

Papa, E.; Kovarich, S.; Gramatica, P. QSAR modeling and prediction of the endocrine disrupting potencies of brominated flame retardants *Chem. Res. Toxicol.*, **2010**, 23, 946-954.

Papa E.; Kovarich, S.; Gramatica, P. On the use of local and global QSARs for the prediction of Physico-Chemical Properties of Polybrominated Diphenyl Ethers *Molecular Informatics*, **2011**, 30, 232–240

Papa, E.; Kovarich, S.; Gramatica P. Development, Validation and Inspection of the Applicability Domain of QSPR Models for physico-chemical properties of Polybrominated DiphenylEthers *QSAR and Combinatorial Science*, **2009**, 28, 790-796.

Papa, E.; Luini, M.; Gramatica, P. QSAR modelling of oral acute toxicity and cytotoxic activity of fragrance materials in rodents*SAR QSAR Environ Res.*, **2009**, 20, 767–779.

Roy, P.P.; Kovarich, S.; Gramatica, P. QSAR model reproducibility and applicability: a case study of rate constants of hydroxy radical reaction models applied to Polybrominated Diphenyl Ethers and (Benzo-)Triazoles *J. Computational Chem.*, **2011**, 32, 2386-2396

Sahlin, U.; Filipsson, M.; Öberg, T. A risk assessment perspective of current practice in characterizing uncertainties in QSAR regression predictions *Molecular Informatics*, **2011**, 30, 551-564

Sushko I.; Novotarskyi S.; Körner R.; Pandey A.K.; Cherkasov A.; Li J.; Gramatica P.; Hansen K.; Schroeter T.; Müller K.R.; Xi L.; Liu H.; Yao X.; Öberg T.; Hormozdiari F.; Dao P.; Sahinalp C.; Todeschini R.; Polishchuk P.; Artemenko A.; Kuz'min V.; Martin T.M.; Young D.M.; Fourches D.; Muratov E.; Tropsha A.; Baskin I.; Horvath D.; Marcou G.; Muller C.; Varnek A.; Prokopenko V.V.; Tetko I.V. Applicability domains for classification problems: benchmarking of distance to models for ames mutagenicity set. *J Chem Inf Model*, **2010**, 50, 2094-2111

Sushko, I.; Novotarskyi, S.; Körner, R.; Pandey, A.K.; Kovalishyn, V.V.; Prokopenko, V.V.; Tetko, I.V. Applicability domain for in silico models to achieve accuracy of experimental measurements *J. Chemometrics.*, **2010**, 24(3-4), 202-208.

Appendix 1: List of Abbreviations

BCF	Bioconcentration factor is the concentration of a particular chemical in a biological tissue per concentration of that chemical in water surrounding that tissue.
(B)TAZ	(Benzo)triazoles
C&L	Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures.
PBDEs	Polybrominated Diphenyl Ethers
PFCs	Perfluorinated chemicals
REACH	Regulation (EC) No 1907/2006 on the Registration, evaluation, authorisation and restriction of chemicals.

Appendix 2: Programme of the CADASTER Workshop

Presentations from the workshop are available at http://www.cadaster.eu/node/119

Thursday, 1st September

13:30-14:00	**Exemplification of the integration of tools within REACH: the CADASTER project**
	Dr. Willie Peijnenburg, RIVM, The Netherlands
14:10-14:40	**Satisfying REACH requirements with OpenTox**
	Dr. Barry Hardy, Douglas Connect
14:50-15:20	**Legislative overview on the use of alternative methods in REACH**
	Evelin Fabjan, ECHA, Finland
15:20-15:50	*Coffee* Break
15:50-16:20	**Technical information on alternative methods**
	Dr. Andrew Worth, JRC, Italy
16:30-17:00	**CADASTER achievements: Database on experimental parameters and (Q)SARs**
	Dr. Mojca Kos Durjava, PHI, Slovenia

Friday, 2nd September

9:00-9:30	**State of the art in QSAR modeling**
	Dr. Alex Tropsha, University of North Carolina, USA
9:40-10:40	**CADASTER achievements: Development and validation of QSAR models**
	Dr. Paola Gramatica, University of Insubria, Italy
	CADASTER achievements: Integration of QSARs with risk assessment
	Dr. Tomas Öberg, Linnaeus University, Sweden
	CADASTER achievements: Dissemination of information in CADASTER project
10:50-11:20	Dr. Igor Tetko, HMGU, Germany
11:40:13:00	*Coffee* Break
	Training lessons for on-line tools that can be used to estimate REACH end-points for chemical compounds and thus decrease the number of animal tests:
	Demonstration of the tools developed in CADASTER (Dr. Igor Tetko, HMGU,
13:00-14:30	Germany)
14:30-16:00	*Lunch* Break
	Training lessons for on-line tools that can be used to estimate REACH end-points for chemical compounds and thus decrease the number of animal tests:
	Demonstration of the models available in the OECD QSAR toolbox (Dr. Emil Rorije,
16:00-17:00	RIVM, The Netherlands)

Appendix 3: Participants list

	Name	Institution
1	Abdulrazak Sahigara Faizan	University of Milano Bicocca
2	Balejikova Jana	Centre for Chemical Substances and Preparations
3	Berleković Vedran	Serbian chemical agency
4	Bhhatarai Barun	University of Insubria
5	Ertürk M. Doga	Boğazisi University Institute of Environmental Sciences
6	Fabjan Evelin	European Chemicals Agency
7	Fioravanzo Elena	S.IN - Soluzioni Informatiche
8	Gramatica Paola	University of Insubria
9	Hardy Barry	Douglas Connect
10	Harju Mikael	Norwegian Institute for Air Research
11	Hulzebos Etje	International Flavors and Fragrances Inc.
12	Jeliazkov Vedrin	Ideaconsult Ltd.
13	Jeliazkova Nina	Ideaconsult Ltd.
14	Kharchevnikova Nina	A.N. Sysin Institute of Human Ecology and Environmental Health
15	Kolar Boris	Public Health Institute Maribor
16	Kos Durjava Mojca	Public Health Institute Maribor
17	Kovarich Simona	University of Insubria
18	Kumar Yadav Dharmendra	Central Institute of Medicinal & Aromatic Plants
19	Lekić Boško	Serbian chemical agency
20	Majer Bernhard	Baxter Innovations GmbH
21	Moeller Ruth	Centre de Recherche Public Henri Tudor
22	Mombelli Enrico	INERIS
23	Moosus Maikki	University of Tartu, Institute of Chemistry
24	Nilsson Sara	Swedish Environmental Research Institute
25	Öberg Tomas	Linnaues University
26	Peijnenburg Willie	RIVM
27	Piir Geven	University of Tartu
28	Rahmberg Magnus	Swedish Environmental Research Institute
29	Rorije Emil	RIVM
30	Rotureau Patricia	INERIS
31	Sushko Yura	Helmholtz Zentrum Muenchen
32	Tetko Igor	Helmholtz Zentrum Muenchen
33	Tropscha Alex	University of North Carolina
34	Van der Geest Bert	Geest s.p., Environmental RA
35	Worth Andrew	Joint Research Centre

Appendix 4: Abstracts of presentations

Presentations from the workshop are available at http://www.cadaster.eu/node/119

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

Professor Willie Peijnenburg (willie.peijnenburg@rivm.nl)
RIVM, Laboratory for Ecological Risk Assessment
Bilthoven, The Netherlands

This presentation consisted of two parts, the first one dealing with an outline on the CADASTER project, the second part dealing with a case study on the development of alternative methods to predict the toxicity of poly- and perfluorinated chemicals (PFCs).

1 – Overview of the CADASTER project.

This part of the presentation first of all highlighted the need for alternative testing within REACH and the need to implement Integrated Testing Strategies (ITS) to efficiently assess the REACH-relevant endpoints, using as limited numbers of test animals as possible. Within ITS, only as a last resort experimental testing is performed. Instead of testing, additional tools and additional information is collected first. This concerns amongst others: Relevant exposure scenarios to assess the possibilities of exposure based waiving, read across options, in vitro data to supplement or even substitute in vivo data, SARs and QSARs, and all other types of existing information that is of help in assessing endpoints. To provide an example of how to integrate various types of information in REACH, the CADASTER project was initiated within the EU-FP7 research programme. CADASTER aims at exemplifying the use of alternative methods for four classes of chemicals: brominated flame retardants, perfluorinated compounds, fragrances, and (benzo)triazoles. In the presentation an overview was given on the goals and aims of CADASTER, the expected outcome, and the various activities within the four workpackages that have been identified.

2 – Aquatic toxicity prediction of poly- and perfluorinated chemicals (PFCs).

Given the fact that PFCs are quite hydrophilic compounds that tend to persist in the aquatic environment, the need to assess the aquatic toxicity profile of PFCs was stressed. It was shown how a combination of tailored experimental design (including the use of principal component analysis, and collection of existing data on as many endpoints and as many different organisms as possible) is to be combined with practical considerations (like possibilities of acquiring the set of chemicals selected in the phase of experimental design) in order to design a test set of chemicals of which the toxicity is to be assessed in the next phase. The toxicity of an extended set of 10 PFCs was assessed towards lettuce, algae, and two daphnid species. For each organism studied, QSARs were derived to predict the toxicity of PFCs on the basis of the data thus generated. The number of carbon atoms in the alkyl chain of the PFCs tested was found to be a suitable indicator of toxicity.

In addition, the possibilities of inter-species extrapolation were demonstrated. Inter-species extrapolation allows prediction of toxicity of PFCs for biological organisms that were not experimentally tested.

Satisfying REACH requirements with OpenTox

Dr. Barry Hardy (barry.hardy@douglasconnect.com), OpenTox Project Coordinator
Douglas Connect
Zeiningen, Switzerland

Predicting the toxic properties of molecules has many important practical implications for society. We want to avoid health damage from the adverse effects of the interactions of foods and drugs in our bodies or from chemical exposure, to reduce environmental damage by chemicals and pesticides, and to support the development by industry of safer products. Safety testing developed in the past century primarily relies on the traditional toxicological science of animal testing, which has significant ethical, scientific and business weaknesses. A new paradigm of 21st century human-oriented testing approaches is now emerging based on a combination of *in silico* and *in vitro* approaches, which combines research and development from numerous fields including computational chemistry, systems biology, stem cell technology, machine learning, microdevice engineering, robotics, assay development, biophysics and clinical research. The new predictive test systems developed from this growing "grand challenge" effort will need to combine evidences from a great variety of data, protocols, and concepts. The combination of these sources of knowledge within an ontology-based mechanistic knowledge-oriented framework to produce reliable test systems demands the development of a semantic web for toxicology.

The OpenTox Framework (1,2) has been developed to support the communication between toxicology resources, based on standard representations of data and metadata, the ability for distributed resources to exchange data and metadata, build and validate models, and generate reporting information relevant for research analysis or risk assessment. I describe the design and semantic architecture of OpenTox and example applications it can currently enable including a) creation and validation of *in silico* models addressing the regulatory requirements of the REACH legislation for chemical safety evaluation (3), b) application in drug discovery infrastructure development and weight-of-evidence library profiling of drug candidate molecules (4), c) infrastructure development for the interdisciplinary research activities of a large cluster of over 70 partners collaborating on the replacement of animal testing in the area of systemic toxicology (5,6), and d) within the FP7 Environment CADASTER project (7).

Recently we worked on a workshop bringing OpenTox solutions to scientists attending the SETAC Africa conference on "Searching for African solutions to Human and Environmental Toxicological Challenges" (8). I reflect on this experience with regards to the potential for OpenTox to help support the educational and research activities of environmental scientists and their collaboration with scientists in other parts of the globe. As OpenTox actively supports the development of Open Source tools and Internet resources, barriers to the application of computer and Internet-based computational toxicology in both European and global contexts should be lowered. Improved integrated computer-based models of health and environmental systems and the consequence of potential perturbations introduced by development and products should provide valuable scientific knowledge supporting better informed decisions.

(1) **OpenTox** - An Open Source Predictive Toxicology Framework, is funded under the EU Seventh Framework Program: HEALTH-2007-1.3-3 Promotion, development, validation, acceptance and implementation of QSARs (Quantitative Structure-Activity Relationships) for toxicology, Project Reference Number Health-F5-2008-200787 (2008-2011). More information at www.opentox.org.

(2) **Collaborative Development of Predictive Toxicology Applications**
Barry Hardy, Nicki Douglas, Christoph Helma, Micha Rautenberg, Nina Jeliazkova, Vedrin Jeliazkov, Ivelina Nikolova, Romualdo Benigni, Olga Tcheremenskaia, Stefan Kramer, Tobias Girschick, Fabian Buchwald, Joerg Wicker, Andreas Karwath, Martin Gutlein, Andreas Maunz, Haralambos Sarimveis, Georgia Melagraki, Antreas Afantitis, Pantelis Sopasakis, David Gallagher, Vladimir Poroikov, Dmitry Filimonov, Alexey Zakharov, Alexey Lagunin, Tatyana Gloriozova, Sergey Novikov, Natalia Skvortsova, Dmitry Druzhilovsky, Sunil Chawla, Indira Ghosh, Surajit Ray, Hitesh Patel and Sylvia Escher
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Full text and supplementary information available in Open Access at:
www.jcheminf.com/content/2/1/7

(3) REACH, http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm

(4) Scientists Against Malaria, http://scientistsagainstmalaria.net/

(5) SEURAT-1, http://www.seurat-1.eu/

(6) ToxBank, http://www.toxbank.net/

(7) CADASTER, http://www.cadaster.eu/

(8) SETAC Africa Conference, 2011, http://cameroon.setac.eu/

Legislative overview on the use of alternative methods in REACH

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One of the main purposes of the REACH Regulation is to ensure a high level of protection of human health and the environment. At the same time, it aims at promoting alternative methods and requires that tests on vertebrate animals are carried out only as last resort. REACH places greater responsibility on industry to manage the risks that chemicals may pose to the health and the environment. It requires manufacturers and importers of chemical substances (≥1 tonne/year) to obtain information on the physicochemical, health and environmental properties of their substances and to use this information to determine and document how these substances can be used safely.

In order to achieve a high level of protection of human health and the environment while limiting the need for additional testing, all available data on the intrinsic properties of a substance, including testing data (*in vivo*, *in vitro*) as well as non-testing data (obtained with (Q)SAR models, grouping of substances, weight of evidence etc.) must be evaluated first. Where available data are not adequate to meet the requirements of the REACH Regulation, additional testing may be needed. Annexes VI to X of the REACH Regulation specify the minimum data requirements for a given substance according to the tonnage for registration purposes. In addition to these specific rules the standard information set may be adapted according to the general rules described in Annex XI of REACH Regulation, which include the use of alternatives to testing on animals (e.g. in cases where testing is not technically possible, or testing does not appear scientifically necessary, or based on exposure considerations).

Whereas the legislation provides the legal framework that registrants need to follow when deciding if and when certain information needs to be delivered, the actual strategies for obtaining this information have been described in extensive guidance documents developed in close collaboration with experts from Member States, industry and NGO's. In addition The European Chemicals Agency (ECHA) provides on its website several practical guides and reports which are aimed to help the registrants in fulfilling their obligations.

ECHA has recently published a report which provides the latest information on the status of non-animal test methods and alternative testing strategies used to generate information for registration purposes. The analysis performed by ECHA shows that the alternatives to testing on animals provided by REACH are being used and registrants so far are not carrying out unnecessary testing. However based on the experience with dossier evaluation so far, it can be said that the justifications that the registrants have provided, for the use of alternative methods to fulfil information requirements, often fall short of what the legislation requires.

This presentation briefly outlined the information requirements under the REACH Regulation, the elements of integrated testing strategies and the applicability of some of these elements (i.e. (Q)SArs and grouping approaches) within REACH. Furthermore, it briefly summarised what was the experience so far with the use of alternatives to tests on animals in the registration dossiers and pointed out some areas where there is a need for improvement.

Technical information on alternative methods

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In this presentation, an overview on the use of technical information on alternative methods was given by Dr. Andrew Worth. The overview focused on the development of internationally harmonized reporting formats for QSAR models (http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/QRF), and in particular on the QSAR Model Reporting Format (QMRF). The QMRF was introduced under REACH to ensure greater consistency in the documentation of models used for regulatory purposes. The current status of the freely accessible JRC QSAR Model Database (http://qsardb.jrc.ec.europa.eu) was presented, a repository of peer-reviewed QMRFs. Model developers were encouraged by Dr. Worth to submit QMRFs to the JRC. A checklist of questions was presented which could be used by regulatory authorities when assessing the adequacy of QSAR model predictions[1]. Dr Worth further referred to a recent initiative, led by the JRC in collaboration with ECHA and the OECD, to develop an OECD-harmonised template for Intermediate Effects (including key events) within Adverse Outcome Pathways (AOPs). It was also indicated that it would be desirable to develop a template for AOPs[2].

[1] Worth et al (2011). A Framework for assessing in silico Toxicity Predictions: Case Studies with selected Pesticides. JRC report EUR 24705 EN.
[2] Subsequent to the CADASTER workshop, the OECD decided to initiate the development of a format for AOPs.

CADASTER achievements: Database on experimental parameters and (Q)SARs

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In this presentation the Overview of activities within WP 2 – Database on experimental parameters and (Q)SARs has been done. Dr. Mojca Kos Durjava presented the tasks within the WP2 and the work that has already been done.

Task 2.1 Collection of existing experimental data - Data search on all endpoints of relevance was performed for the environmental risk and hazard assessment for four classes of chemicals selected in this project (Brominated flame retardants, Fragrances, Perfluorinated chemicals, Triazoles and Benzotriazoles). Physicochemical properties, environmental fate parameters, and aquatic and terrestrial ecological effect parameters are included, among other available toxicity data. This task was carried out by means of a literature search, supplemented with searches of existing databases on risk and hazard assessment parameters, like IUCLID, AQUIRE, etc. Thereupon, additional data were collected from industry sources and regulatory agencies (Dupont, RIFM).

Task 2.2 Collection of (Q)SAR models and non-testing approaches - A survey of the existing QSAR/QSPR models for the four classes of chemicals selected in this project has been completed. At the moment, just a few QSAR models specifically developed on the four chemical classes of compounds studied in CADASTER, have already been published. QSAR models are predominantly developed for non-SIDS endpoints, such as endocrine disruption (for BFRs and PFCs) or skin sensitization (for fragrances). There is only one QSAR model based on acute toxicity to fish which is developed for a large data set containing a few substituted triazoles. QSPR models are available only for some SIDS physico-chemical properties of BFRs (Henry's low constant, vapor pressure, water solubility, $LogK_{OW}$, photodegradation rate), while for the other three classes of chemicals EPI Suite models are the only tools available to predict SIDS physico-chemical properties.

An short overview was given of the non-testing options given under REACH to either replace experimental testing, or to strengthen confidence in experimental results.

Task 2.3 Generation of new data - The testing is almost concluded and has been done on the selected Polybrominated Dipheylethers - PBDEs, Fragrances, Perfluorinated chemicals - PFCs, Triazoles and Benzotriazoles - (B)TAZ for the endpoints of relevance for the project. Bioaccumulation in sediment was tested for relevant PBDEs, different ecotoxicological test were performed for fragrances, PFCs and (B)TAZ and biodegradation study for selected fragrances and (B)TAZ was performed. Some preliminary results were presented.

State of the art in QSAR modeling

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After nearly five decades "in the making", QSAR modeling has established itself as one of the major computational molecular modeling methodologies. QSAR modeling can be characterized by a collection of well-defined protocols and procedures that enable the expert application of the method for exploring and exploiting ever growing collections of biologically active chemical compounds. In this presentation, we have examined some of the most critical QSAR modeling routines that we regard as best practices in the field. We discussed these procedures in the context of integrative predictive QSAR modeling workflow that is focused on achieving models of the highest statistical rigor and external predictive power. Specific elements of the workflow consist of data preparation including chemical structure (and when possible, associated biological data) curation, outlier detection, dataset balancing, and model validation. We especially emphasize the critical importance of chemical structure curation and normalization; procedures used to validate models, both internally and externally; and the need to define model applicability domains that should be used when models are employed for the prediction of external compounds or compound libraries.

We have also discussed the applications of QSAR modeling to computational chemical toxicology, especially for *in silico* prediction of *in vivo* toxicity endpoints using so called hybrid chemical/biological descriptors. While experimentally-derived toxicity data has been difficult to obtain on a large number of chemicals in the past, recent efforts by the Tox21 consortium of the US Federal agencies are generating quantitative in vitro toxicity screening data on thousands of environmental chemicals in hundreds of experimental systems. In addition, publicly accessible toxicogenomics data collected on hundreds of chemicals provide another dimension of information-rich molecular information that is potentially useful for modeling. Thus, we have hypothesized that a combination of chemical structural information, in vitro screening, and/or toxicogenomics data can be used to generate quantitative models to predict human toxicity and carcinogenicity. Using several case-studies described below, we have illustrated the benefits of the "hybrid" modeling approach, namely improvements in the accuracy of models, enhanced interpretation of the most predictive features, and expanded applicability domain for wider chemical space coverage.

To properly realize the joint benefits of bioinformatics- and cheminformatics-based approaches, several strategies can be considered. The simplest way is to utilize a consensus of QSAR and biological models that were derived independently. However, this requires models of similar predictive quality, which is not always the case, especially when the study design was biased towards either biology or chemistry. This problem can be overcome by a "hybrid" approach, in which biology-derived features and chemical structural properties are pooled into a descriptor matrix which is then used for modeling (Low et al. 2011; Sedykh et al. 2011; Zhu et al. 2008). Finally, in some cases, a hierarchical approach can be applied, when chemicals are first partitioned in groups based on their *in vitro*/*in vivo* relationships.

Traditional QSAR models are then trained to differentiate chemicals between those groups, at the same time, local QSAR models are derived to predict *in vivo* effects within each group (Zhu et al. 2009).

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CADASTER achievements: Development and validation of QSAR models

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In the **Overview of activities within WP 3** - Development and validation of QSAR models Prof. Paola Gramatica presented the Tasks of the WP3 and the work already done in the Project.

In particular, for **Task 3.1 - Preparation of the chemical structures and molecular descriptors database for the chemicals of the four selected classes:** the database has been prepared starting from the minimum energy conformations of the molecules obtained by Hyperchem, calculation of Dragon and CADASTER descriptors.

The extensive literature search, performed in **Task 3.2 - Evaluation of existing QSARs,** and **Task 3.3 - Gap analysis,** has highlighted the need of the development of local QSAR models specific for the 4 CADASTER classes of chemicals.

In **Task 3.4 - Prioritization for experimental tests,** also toxicity endpoints for rodent have been used for the development of QSAR models and multivariate analysis for the prioritization of chemicals more hazardous for experimental tests in WP2.

In **Task 3.5 - Development of new QSARs.** Various local QSAR models for different end-points (physico-chemical properties and toxicity end-points) have been developed for the 4 classes of chemicals and verified for their very high applicability to hundreds of chemicals of the relative class of compounds in the ECHA pre-registration list. Some of these models have been already published in peer-reviewed international journals (12 by UI, 1 by LNU and 1 in common by UI-LNU-HMGU-IDEA) and presented in several international meetings. The better results in predictivity of these local models in comparison to EPI Suite predictions, obtained from a general model, have been demonstrated with an example of LogKoa. Some of the already published models have been uploaded in the CADASTER web (WP5).

The **Task 3.6 - Development of multi-model approaches (consensus modeling) and** the **Task 3.7 - External Validation of QSAR models with experimental data from the Project** will be the subject of the next work.

In conclusion, the main aim of WP3 in CADASTER is: a) to prioritize chemicals for focusing experimental tests, b) to develop local QSAR models, specific for the 4 classes of emerging pollutants, which are topic of the Project, models that are all externally validated and verified for their structural Applicability Domain to chemicals of the same classes without experimental data.

CADASTER achievements: Integration of QSARs with risk assessment

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The CADASTER work package 4 aims to integrate QSAR models in risk assessment and evaluate tools, economic impact, and legal framework. The work package will also provide a synthesis of research findings and recommendations for prioritization. These sub-tasks are addressed and reported separately. In the first sub-task, QSARs in a probabilistic risk assessment framework, a literature review has been completed and case-studies are well under way, both to characterize uncertainty in model predictions and implementation in multimedia fugacity models. Here we aim to discuss the relevant questions and bring predictive uncertainty into a risk assessment perspective and illustrate various methods. The empirical evaluation is accomplished using models and data from other CADASTER work packages. How QSAR uncertainty affects the risk assessments is a key issue to address. An Excel-based application for targeted risk assessment (ECETOC TRA tool) has been evaluated and validated against a level III fugacity model. The evaluation report issued in 2010 focuses mainly on the usability and needs for improvement in this respect. Possibilities for assessing costs of chemical impacts were investigated in a case study on impacts of PBDEs on the peregrine population of California. The impacts were analyzed using a probabilistic population model and three different exposure scenarios, were the valuation of impacts was assessed by the replacement costs with captive-bred birds. A final report has been submitted for this sub-task in 2011. Work in progress and remaining deliverables include reports on application of QSAR models for probabilistic risk assessment and guidance, QSAR models in the legal framework, and synthesis and recommendations for prioritization.

CADASTER achievements: Dissemination of information in CADASTER project

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In this presentation the overview of the activities in CADASTER project for dissemination of the project results was given by Dr. Igor Tetko. Three web sites were developed, which cover different functionality of the project.

The first web-site, http://www.cadaster.eu is a portal for news and deliverables, articles, posters and oral reports. Each participant has an own web-page where he/she can provide information related to the CADASTER activities. This site was used as a main portal for environmental toxicity prediction challenge, which had more than 100 participants from the world. The CADASTER team members are actively involved in training of students in environmental chemoinformatics within the FP7 MC ITN project Enviromental Chemoinformatics http://www.ecoitn.eu as well as contributed courses during "Achievements and applications of contemporary informatics, mathematics and physics" schools in Kiev. The CADASTER newsletter provided recent information about the latest achievements of the project and it is available as http://www.cadaster.eu/newsletter.

The second web-site, QSPR-THESAURUS http://www.qspr-thesaurus.eu is based on the On-line Chemical Modeling Environment (OCHEM), which is developed and supported by eADMET GmbH http://www.eadmet.com. During the project, HMGU group has customized the web interface and added several tools in order to fulfill requirements of CADASTER participants. Igor briefly mentioned the main functionality of the QSPR THESAURUS and overviewed functionality of the web site. The models available at the QSPR THESAURUS web site also estimate applicability domain (AD) of the models, thus allowing users to decide whether they should use the predictions given by such models.

The third site, http://mopac.cadaster.eu has been developed to support 3D structure generation for the project. It is based on BOINC platform and takes advantage of user-contributed CPU time to find conformations of molecules with the minimum energy. Currently, the database contains optimized conformations for more than 200k molecules optimized using MOPAC AM1 semi-empirical calculation method. These calculations were contributed by 1011 users with total duration of 11,14 years of CPU time.

Training lessons for on-line tools that can be used to estimate REACH end-points for chemical compounds and thus decrease the number of animal tests:

Demonstration of the tools developed in CADASTER

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The tools developed in CADASTER project were demonstrated. As it was mentioned, the QSPR-THESAURUS http://www.qspr-thesaurus.eu is based on the On-line Chemical Modeling Environment (OCHEM), which is developed and supported by eADMET GmbH http://www.eadmet.com. During the project, we provided customization of the site to meet requirements of CADASTER project participants. We developed tools to upload linear models; there is a built-in support of (Q)SAR Model Reporting Format (QMRF) format; web services and standalone tools to access CADASTER models were also developed; database of 3D structures as well as integration of OpenTox API (similarity search, Applicability Domain estimations) were provided. The functionality of the web site was overviewed in details.

Data: the web site stores detailed information about the data. Each experimental record can have names, publication source, evidences, position in the article. This allows for an easy verification of experimental data from scientific publications. Users can easily verify them in case of any doubt about the data quality. The user can provide detailed description of experiment by specifying conditions. In case if some properties are not available, the users can also to introduce them as well as conditions, units. He demonstrated how user can do it just in few clicks. A possibility to upload single records as well as set of records prepared in Excel file using batch upload was explained.

Datasets: The concept of datasets was explained. The datasets are used to select data for batch operations, such as addition, deletion or changes of information, e.g. providing new experimental conditions, changes of the introduced units, etc. They are also used to develop models and use them to predict sets of molecules.

Models: The modeling tools, namely linear regression and Partial Least Squares methods were explained. The workflow to create and validate new models was demonstrated. The use of leverage to estimate applicability domain of models was shown. Igor also demonstrated how the developed models can be used to predict new data starting from chemical structure or names and how the prediction results should be interpreted. Upload of linear models was also demonstrated.

Tutorial: The detailed steps how to upload and reproduce linear BCF model were provided. The details of the tutorial are available at http://www.cadaster.eu/maribor.

Experimental design: Iurii has demonstrated how the developed web-site can be used to optimally select chemical compounds for experiments. This functionality is indispensable when a property must be estimated for a large number of chemical compounds but the budget for experimental measurements is limited and only a small number of measurements can be conducted. Two approaches for experimental design have been implemented on the web-site and demonstrated during the Iurii's tutorial: the classical approach (D-Optimal design) and the new approach (PLS-Optimal design), which was developed by HMGU and LNU partners.

Panel Discussion on the use of QSARs in REACH

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1. What are that major barriers for a wider use of alternative and in particular *in silico* methods in REACH?
2. What is your (industry) experience with the use of *in silico* methods for REACH?
3. As a regulator, which criteria will be important for you to accept the *in silico* model results?
4. As an industry, will you be willing to share your experimental data for QSAR/QSPR models development for REACH?
5. What are your recommendations and how can we improve our tools?
6. When Daphnia (and algae) can also predict fish toxicity this would limit fish testing. Which modes of actions for the 4 groups could result in additional fish toxicity compared to algae and daphnia?
7. The uncertainty of QSAR results becomes important when they are close to the cut off values of C&L and PBT assessment because of regulatory implications. Because under REACH safe use of chemicals needs to be ensured via risk characterization the regulatory implications on C&L may become less important but not for PBT?
8. Can the BCF models predict the BCF of reactive chemicals (e.g. hydrolyzing (esters) or protein binders) or readily biodegradable chemicals to potentially decrease the probability for bioaccumulation?
9. It seems there is a lack of environmental data for the four selected CADASTER chemical classess. Most of the CADASTER QSAR models developed are an animal toxicity models. What can be done to connect these two, any suggestion from REACH/ECHA?
10. Regarding proprietary data from industry: Can't it be used to use models keeping data and model still proprietary to predict the properties? The statistics of the model could be shown to know the model is valid.
11. Is there a future for traditional QSAR in regulatory toxicology?