OSIRIS Newsletter

No. 10 September 2011

In this Issue:

- Fourth OSIRIS Annual Meeting
- OSIRIS ITS Stakeholder Workshop
- OSIRIS at SETAC Europe
- OSIRIS Pillar 2 Meeting
- Final OSIRIS Meeting
- OSIRIS Methods and Models Developed
- Public Software and Data from OSIRIS

Photo: Andrea Richarz

Contents:

Fourth OSIRIS Annual Meeting

Photos: Sebastian Stremptel

Fourth OSIRIS Annual Meeting

The Fourth OSIRIS Annual Meeting was held **on Wednesday 30 March–Friday 1 April 2011 in Barcelona, Spain,** at the University of Barcelona campus in the Barcelona Science Park.

It was hosted by the OSIRIS partner Universitat Rovira i Virgili (URV).

On the agenda were:

- Results of the 4th project year
- Integrated Testing Strategies implemented in the OSIRIS Webtool
- Planning for the last months of the project and beyond, and
- Intra- and inter-Pillar discussions.

Pillar Results

Results from the different workpackages and Pillars were reported to the plenum.

In **Pillar 1**, this included an update of the BCF waiving scheme, a report on alternative modules for the BCF ITS, as well as a presentation of ChemProp and its interface to the OSIRIS Webtool with applicability domain consideration. Latest results on structural alerts, read-across and *in silico* application domain were presented.

Pillar 2 gave an update on mammalian toxicity data collated including data quality and applicability domain assessment, tools for environmental hazard assessment as well as on results regarding across-species relationships and alternative approaches.

The latest developments of models for assessment of environmental exposure and fate, as well as exposure-based waiving considerations for human exposure including toxicokinetic models were presented by **Pillar 3**.

In addition to the ITS presentations for the different endpoints, **Pillar 4** discussed ITS optimisation, implementation and acceptance and demonstrated the general functions of the Webtool.

Pillar 5 reported on a case study on PBT assessment, the latest results regarding risk assessment of drinking water contaminants, case studies with the OSIRIS ITS, as well as on an overview on available software models for mutagenicity and a case study on selected applicability domain methods. Furthermore, results of a comparison and evaluation of models for workplace exposure were presented.

A summary of the last OSIRIS Training Course organised by **Workpackage 6** was given.

Photos: Sebastian Strempel, Andrea Richarz

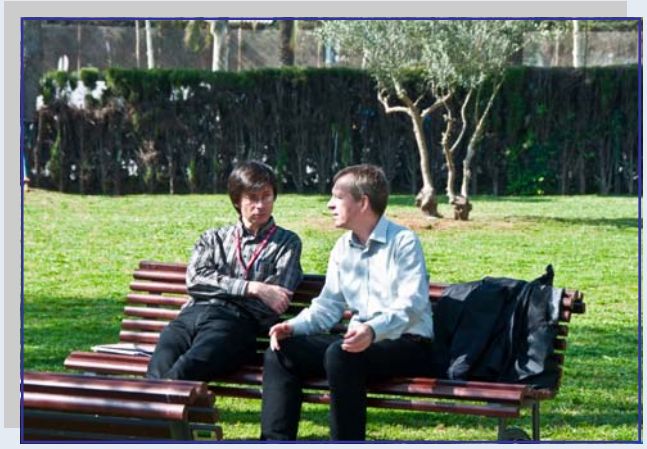
Fourth OSIRIS Annual Meeting

ITS Presentations

The ITS developers presented the status of the ITS implemented in the OSIRIS Webtool for the five endpoints:

- Skin sensitisation
- Repeated dose toxicity
- Mutagenicity & carcinogenicity
- Bioconcentration factor
- Aquatic toxicity.

Background information on the ITS concepts was given, the latest developments were reported, the ITS were demonstrated with examples and cases studies and then discussed in the plenum. Moreover, a summary of the feedback from the questionnaires distributed at the recent ITS Stakeholder Workshop was given to the plenum, and further improvements to be considered in the last months of the project were discussed.



Break-Out and Final Discussions

Details of further developments were discussed in more detail in two groups focussed on human health endpoints or environmental endpoints, respectively.

Furthermore, the planning and intra/inter-Pillar interactions for the final months of the project were discussed in Pillar working groups.

The final plenum session summarised the major issues for the remaining six months of the project and the timeline of the lasts steps to be taken. Furthermore, suggestions were made regarding the availability and maintenance of the OSIRIS models and tools after the end of the project .

Beyond the Meeting Presentations...

Last but not least, there were further opportunities for discussions outside the meeting rooms, while enjoying the Barcelona sun and food.

All delegates were very happy to taste many sumptuous Catalan dishes including original paella at the traditional meeting dinner organised by the URV hosts.

And those who were so lucky as to have some more time after the meeting had further opportunities to enjoy the rich culture of the city of Barcelona, its Modernisme buildings and parks, and possibly even the sunny beach, a new aspect of an OSIRIS meeting in March!

Photos: Sebastian Strempel, Andrea Richarz

OSIRIS ITS Stakeholder Workshop

Around 50 stakeholders from industry, regulatory authorities and academia attended the **OSIRIS ITS Stakeholder Workshop** on Integrated Testing Strategies (ITS) on **8–9 March 2011** at the Helmholtz Centre for Environmental Research – UFZ in **Leipzig**, Germany. It was organised by the OSIRIS partner DIALOGIK in close cooperation with the Co-ordinator UFZ.

The stakeholders were invited to test the methods and ITS developed within OSIRIS and to give feedback for the final phase of the project.

The workshop was divided into five sessions according to the **five ITS endpoints** implemented in the OSIRIS Webtool:

- Skin sensitisation
- Repeated dose toxicity
- Mutagenicity & carcinogenicity
- Bioconcentration factor
- Aquatic toxicity.

Background information on the ITS and their underlying concepts were presented and the ITS Webtool demonstrated with examples, followed by practical application and exercises and discussion in the plenum. Feedback from stakeholders was collected through several questionnaires. All together 128 questionnaires were completed and submitted during the workshop.

The majority of the responses indicated that the OSIRIS Webtool is user-friendly and the navigation clear and easy. The results have been clearly documented, are readily accessible, understandable and reasonable.

Photos: Andrea Richarz

The OSIRIS Webtool for the five endpoints considered is thus anticipated to be an easily accessible and transparent webtool helping stakeholders to understand the testing strategies, and to support the development of integrated and non-testing toxicity methods. It can integrate results from additional local software such as "Derek", "ToxTree" and "ChemProp", it will thus be very convenient and helpful for users to combine different results. It has been pointed out that as a consequence a standard format should be used for the import and export of data.

It has also been suggested to compile a comprehensive documentation and report for each endpoint, the parameters used and referring to the ECHA guidelines, in the last phase of OSIRIS. A comprehensive output-report document for the assessment should be provided, describing which input-parameters were used and indicating the underlying algorithm.

The participants stated that they would use the OSIRIS Webtool for strategy development and to get a better idea how information sources add statistical "weight of evidence". The OSIRIS Webtool is seen as a supporting instrument rather than a stand-alone software to avoid animal testing, and to rely on expert judgement.

The availability of the OSIRIS Webtool and the extensive knowledge integrated in the ITS beyond the end of the project has been pointed out as an important issue.

OSIRIS at the SETAC Europe 21st Annual Meeting

Joint presentation of the OSIRIS BCF working group

The OSIRIS Integrated Testing Strategy (ITS) for bioaccumulation, its modules and their implementation in the OSIRIS Webtool, has been presented in a dedicated poster corner at the SETAC Europe 21st Annual Meeting on 15–19 May 2011 in Milan, Italy. A general overview was provided in a plenary presentation based on the OSIRIS report "Integrated testing strategies (ITS) for bioaccumulation: hierarchical scheme of chemistry-driven methods", authored by the OSIRIS partners of the bioconcentration factor (BCF) working group and presented by M. Nendza. The poster corner addressed 12 topics, detailing alternative methods and approaches:

ITS:

- Integrated Testing Strategy (ITS) to optimise the assessment of bioconcentration under the REACH framework
  (A. Lombardo, A. Roncaglioni, M. Nendza, H. Segner, S. Jeram, E. Benfenati)

Existing data:

- Sources and data quality of the existing data for bioconcentration
  (A. Lombardo, A, Roncaglioni, M.I. Petoumenou, M. Nendza, E. Benfenati)

In silico classification methods:

- Screening for low aquatic bioaccumulation: physico-chemical constraints
  (M. Nendza, T. Herbst)

Photos: Wolfgang Janzen

- Use of conditional inference trees in support of B and non B classification for waiving of experimental BCF testing
  (S. Strempel, M. Nendza, M. Scheringer, K. Hungerbühler)
- A cost-based classifier for bioaccumulation assay waiving
  (R. Rallo, A. Fernandez, F. Giralt)

In silico QSAR methods:

- Applicability and performance evaluation of QSAR models for bioconcentration in fish
  (A. Lombardo, A. Roncaglioni, M.I. Petoumenou, M. Nendza, A.P. Toropova, A.A. Toropov, R. Kühne, A. Franco, E. Benfenati)
- Models to estimate the BCF from octanol/water partition coefficient – validation and applicability domain
  (R. Kühne, R-U. Ebert, S. Strempel, M. Scheringer, G. Schüürmann)
- Read-across model to estimate the BCF in fish from data for similar compounds
  (R. Kühne, R-U. Ebert, G. Schüürmann)

Physiological models:

- The challenge of testing toxicity and bioaccumulation of ionising compounds at various pH
  (S. Trapp)

OSIRIS at the SETAC Europe 21st Annual Meeting

***In vitro*/reduced *in vivo* methods:**

- Integrated testing strategies (ITS) for bioaccumulation: *in vitro* optimisation modules (H. Segner, C. Lany, A. Hawliczek, M. Nendza, A. Lombardo, A. Roncaglioni, E. Benfenati)
- Integrated testing strategies (ITS) for bioaccumulation: 3R-directed optimisation of *in vivo* BCF testing (H. Segner, A. Hawliczek, M. Nendza, A. Lombardo, A. Roncaglioni, E. Benfenati)

Photo: Wolfgang Janzen

The dedicated OSIRIS bioaccumulation poster corner was a great success and attracted plenty audience. The lively discussions concerned methodological issues, applicability domains and margins of uncertainty.

Additionally, a generic poster with general OSIRIS information, i.e. project structure, objectives, and partners, introduced the Webtool and complemented the scientific presentations. Flyers and brochures were distributed to invite potential stakeholders to the final presentation of the OSIRIS results in September 2011 in Leipzig, Germany.

OSIRIS Pillar 2 Meeting in Piran

The need for biology in categorising and predicting chemical toxicity

On 8–9 September 2011, an OSIRIS Pillar 2 Meeting was held in Piran, Slovenia, organised by OSIRIS partner IVZRS.

The main goal of the two day workshop was to bring together scientists involved in the OSIRIS project Pillar 2 and discuss the use of biological information in predictive toxicology and qualitative/quantitative structure relationship (QSAR) development.

The following issues were discussed:

- Sense and nonsense of biomarker and -omics information for predictive ecotoxicology (Ronny Blust)
- The importance of mode of action information for predictive (eco)toxicology (Monika Nendza)
- *In vitro* methods and data for predictive ecotoxicology (Helmut Segner)
- *In vivo* toxicity data in predictive ecotoxicology (Kees van Gestel).

In our attempt to predict adverse chemicals' effects for the purpose of classification and risk assessment we are confronted with a large diversity in chemical structures and properties and also with a huge diversity in biological species and targets. The challenge is therefore to look for unifying principles in this otherwise very diverse landscape in terms of structures and functional organisation. A successful solution can only come from an approach that combines and integrates chemical and biological understanding in a robust and relevant manner.

OSIRIS Pillar 2 Meeting in Piran

Comparable to chemical read-across that uses structural similarities among chemicals to conclude that they have similar toxic mode of action (MoA), similarities in biological response profiles can function as biological read-across. This principle is applied, for instance, in the US ToxCast programme established in the field of human toxicology. One of the main challenges is to determine an optimal strategy to use the biological information obtained from molecular (omics), *in vitro* and *in vivo* systems to assign a compound to a MoA category and predict its toxicity.

Reliable assignment of chemicals to MoAs is a limiting factor in the application of QSAR approaches. Having additional information for MoA assignment available from biological profiling will improve the power of predictive toxicology. MoA is not a constant compound-specific property. It depends on physicochemical properties and structures of the toxicants as well as on biological receptor-specific characteristics, e.g. the presence of specific targets, and it is affected by the concentration and duration of exposure. This also implies that chemicals can have multiple MoAs. The different sensitivities and responses of species related to MoA means that no uniform modelling scheme is applicable to all endpoints. Because of the variability in MoA of chemicals between species, there cannot be one representative species. The relative sensitivities of species to compounds vary depending on their particular MoAs in those species, which again are determined by the presence/absence of biomolecular and physiological targets for specific effects. As a consequence, the same compound may be either a baseline or excess toxicant towards different species as illustrated by species-specific deviations from baseline QSARs by MoA. Likewise, the same compound may be either a baseline or excess toxicant for the same species depending on exposure concentration or duration.

Biological data are also key to the establishment of adverse outcome pathways (AOPs). AOPs connect molecular responses to toxicants with adverse effects of the toxicants on organisms and higher ecologically important levels. Within this context MoA information is currently explored for its potential as a qualitative categorising instrument. Both AOP and MoA information assists in developing rational and targeted testing of chemical hazards. An example is the tiered testing strategy for endocrine disruptors suggested by the US EDSTAC Committee which includes biological endpoints as "signposts" indicating the relevant toxic processes, e.g. hormone receptor binding as a pathway through which endocrine disrupting chemicals can induce adverse effects is an example of such an approach. Towards the future the MoA and AOP approaches should develop into more quantitative instruments which may also be used to link effects manifested in an early phase at the molecular and cellular levels to effects at higher levels of structural and functional organisation which are of direct ecological relevance and can be used in a weight of evidence based hazard and risk assessment strategy.

The meeting was concluded with an agreement to prepare a detailed report to be published.

OSIRIS Results Highlights

QSARs for soil ecotoxicity (Partner VU)

Dep. of Animal Ecology, Faculty of Earth and Life Sciences, Vrije Universiteit, Amsterdam, The Netherlands

Non-polar organic compounds exert their toxicity through membrane disruption, resulting in serious effects on aquatic and terrestrial organisms at the individual and population level. The primary physicochemical property of chemicals that best can explain their narcotic mode of action is their **lipophilicity** (log K_{ow}), which is successfully applied in **quantitative structure-activity relationship** (QSAR) development.

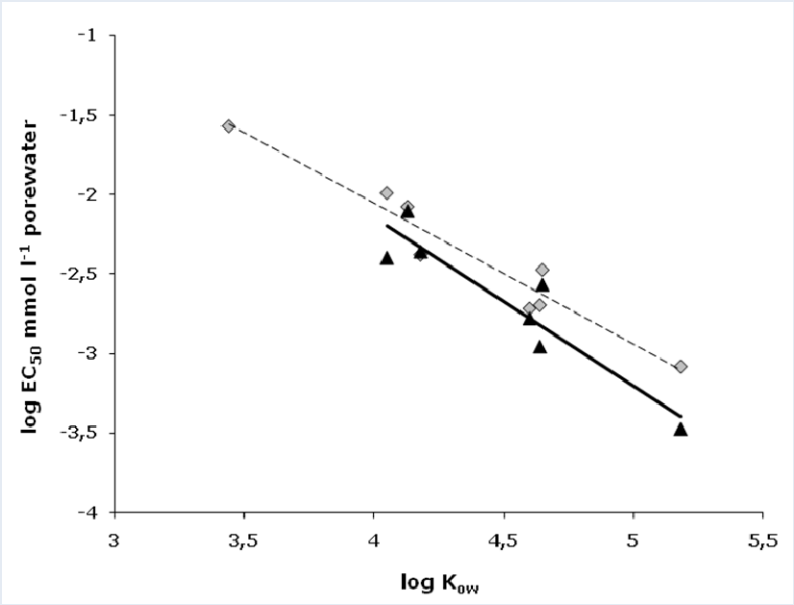
In soil, the toxicity of organic pollutants is governed by the bioaccessible concentration in the porewater, which can be estimated from total soil concentrations using the **organic carbon-porewater partitioning coefficient** (log K_{oc}). Therefore, lipophilicity and soil sorption coefficient (with the organic carbon fraction of the soil (f_{oc})) may describe the toxicity of non-polar substances to soil organisms.

The parthenogenetic soil dwelling springtail *Folsomia candida* is a widely used test organism with a battery of possible endpoints varying from survival, reduction in reproduction and gene response to soil contamination. Nevertheless, no QSARs are available to predict toxicity of organic chemicals for this soil organism.

Folsomia candida

Chronic soil toxicity tests have been performed with *F. candida* in natural LUFA 2.2 soil, with known organic carbon content, using series of different chemicals, including eight **chlorinated benzenes**. A linear regression QSAR was developed for concentrations causing 50% reduction of reproduction (EC_{50}). A second batch of soils was spiked with concentrations corresponding with the respective EC_{50} values of the test chemicals. The free (available) fraction of the chemicals in these soils was determined with **solid-phase micro-extraction** (SPME) to enable for a comparison of estimated porewater concentrations with actual measured concentrations.

Both based on estimated and on measured porewater concentrations, the chlorobenzenes show baseline toxicity, with a negative relationship of EC_{50} (in mmol/l) with lipophilicity and increasing degree of chlorination of the benzene ring (see Figure). SPME measurements gave lower porewater concentrations than estimated using log K_{oc} values derived from the literature.



Quantitative structure-activity relationships showing EC_{50} values for the toxicity of chlorobenzenes to *Folsomia candida* based on porewater concentrations (in mmol/l) estimated (grey diamonds and dashed line) and measured using SPME (black triangles and solid line).

OSIRIS Results Highlights

Furthermore, the difference between estimated and measured concentrations increased with increasing log K_{ow}. Therefore, the prediction of EC_{50} values and resulting QSARs becomes less accurate for highly lipophilic compounds (log K_{ow} >5.2).

Further research includes chloroanilines and chlorophenols and includes the assessment of membrane-water partitioning coefficients to enable description of the toxicity of all different chemicals with a single QSAR.

Additional information: Janssens TKS, Giesen D, Mariën J, Van Straalen NM, Van Gestel CAM, Roelofs D 2011. Narcotic mechanisms of acute toxicity of chlorinated anilines in *Folsomia candida (Collembola)* revealed by gene expression analysis. Environment International 37 (5): 929–939

Formation of Mechanistic Categories and Local Models for the Prediction of Toxicity (Partner LJMU)

School of Pharmacy and Chemistry, Liverpool John Moores University, UK

A paper describing some of the results for the OSIRIS project and presented at the 7th World Congress on Alternatives and Animal Use in the Life Sciences (WC7) in Rome, August 2009, has been selected as one of the "highlights" in the Congress proceedings (Cronin et al 2011). The paper focuses on practical issues arising from work in the project relating to the ability to group compounds together to allow for read-across and create "local" i.e. chemical category and mechanism specific quantitative structure-activity relationship (QSAR) models for the prediction of toxicity.

The paper describes a number of methods to group chemicals, as well as the advantages of read-across. Work within OSIRIS has assisted in techniques to group chemicals including the use of chemical analogues and similarity as well as profilers for mechanisms and modes of action. The topic is illustrated with reference to forming categories for skin sensitisation. It is well established, e.g. through work in the OSIRIS project, that profiling works best when performed using molecular fragments associated with electrophilic reactivity. Other work in OSIRIS has assisted in the formation of database of experimental *in chemico* data which can be used to define the boundaries of reactive mechanisms and predict potency (Schwöbel et al 2011).

The paper by Cronin et al describes the advantages of local models (following category formation) and QSARs. Advantages include the increasing availability of tools to develop local QSARs and form categories; their increasing acceptance across industry and regulatory agencies due to their transparency and mechanistic interpretability; the fact the methods are easy to develop and describe especially in terms of the OECD Principles for the Validation of (Q)SARs. Inevitably, a number of disadvantages need to be recognised and appreciated including that local QSARs and categories will need to be created on a case-by-case basis requiring expert judgment; they are limited by the availability of toxicity data to populate the category or chemical grouping as well as lack of knowledge regarding mechanisms or modes of action. The OSIRIS project provided considerable guidance and a number of case studies to assist the development of such models.

More information:

Cronin MTD, Enoch SJ, Hewitt M, Madden JC 2011. Formation of mechanistic categories and local models to facilitate the prediction of toxicity. ALTEX 28: 45-49

This paper is available freely from: http://www.altex.ch/resources/rEB3_Cronin2.pdf.

Schwöbel JAH, Koleva YK, Enoch SJ, Bajot F, Hewitt M, Madden JC, Roberts DW, Schultz TW, Cronin MTD 2011. Measurement and estimation of electrophilic reactivity for predictive toxicology. Chemical Reviews 111 (4): 2562–2596

OSIRIS Results Highlights

Stakeholder Interviews on ITS Acceptance (Partners WUR, DIA)

Wageningen University, Environmental Economics and Natural Resources Group, The Netherlands;
DIALOGIK, Non-profit Institute for Communication and Cooperation Research, Stuttgart, Germany

Integrated Testing Strategies (ITS) are sequential combinations of testing and non-testing methods, which are expected to allow for a more resource-efficient hazard and risk assessment process of chemicals (Jaworska et al. 2010). The usefulness of ITSs crucially depends on their acceptance and application by various stakeholder groups, for example chemical industry, scientific organisations and regulatory authorities. Although a lot of attention has been paid to the problem how to develop and apply ITSs, there is hardly any information about the stakeholders' view on ITS use and acceptance. As part of the OSIRIS project the aim of our study was, therefore, to gain insight into what stakeholders consider most relevant with respect to five selected topics, (i) the definition of ITS, (ii) ITS advantages, (iii) limitations, (vi) ITS implementation and acceptance, and (v) needs for further research.

The analysis was performed in two steps. First, semi-structured interviews with 19 members from chemical industry, scientific organisations, consultancies, NGOs and regulatory agencies were conducted. Second, the interviews were evaluated using qualitative data analysis methods. This identified a set of "core theme" categories that stakeholders consider most relevant (see Table), each of which consisting of several sub-categories.

Core themes identified for the whole sample of stakeholders

Theme category	Frequency of theme reference
hazard/risk information sources	162
uncertainty	154
costs	153
endpoint	125
decision-making	121
learning	118
stakeholders	118
experimental animals	99
future perspective	95
ITS functional characteristics	88
ITS conceptual structure	62
assessment and measurement	40
information requirement	30
REACH/regulation	27
data compilation	24
ITS outcome target	22
knowledge	17
information documentation	15
ITS terminology	12

In addition, stakeholder-specific patterns concerning core themes addressed were analysed. This allowed for identifying areas of consensus and debate across stakeholder groups. Stakeholders showed quite similar perceptions regarding the definition of an ITS. Here, stakeholders from industry, regulatory agencies and science pointed to the iterative structure, using different alternative methods for data generation complemented by a weight-of evidence approach, to be a key characteristic of an ITS. Members from consultancies and interest groups understood ITS as tools for facilitating decision-making. We observed more disagreement across stakeholders regarding the other topics addressed in the interviews. Interestingly, stakeholder perceptions differed considerably with respect to ITS implementation and acceptance. While members from industry and interest groups considered the limited cost-saving potential, the lacking validation of ITS and the unclear policy acceptance of ITS to hamper ITS implementation, interviewees from regulatory agencies and consultancies emphasised the need for further learning and training in order to build confidence and trust in ITS. Stakeholders from science, to the contrary, pointed out that further guidance on ITS application will be required.

Although our study can only provide a first snapshot of stakeholder views, it underlines that communication between stakeholders on factors triggering and hampering ITS use is important and deserves more attention in order to strengthen ITS implementation on a broader scale.

Reference

Jaworska J, Gabbert, S, Aldenberg T 2010. Towards optimization of chemical testing under REACH: A Bayesian network approach to Integrated Testing Strategies. Regulatory Toxicology and Pharmacology 57: 157-167.

OSIRIS Results Highlights

Acute Fish Toxicity Prediction for Organic Compounds by Quantitative Read-Across (Partner UFZ)

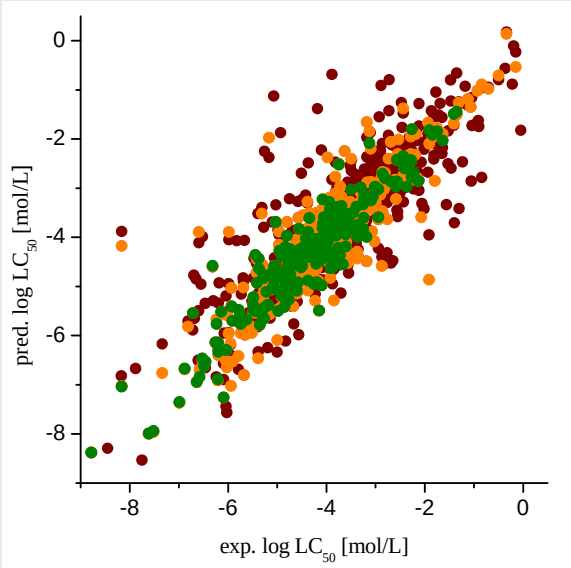
Helmholtz Centre for Environmental Research - UFZ, Dep. Ecological Chemistry, Leipzig, Germany

Developed acute toxicity to fish is part of the ecotoxicological assessment in the context of a regulatory hazard evaluation. REACH requires the evaluation of acute fish toxicities for chemicals with annual production volumes above 10 t/a.

With the increasing interest in reducing or replacing animal testing, both *in vitro* assays and *in silico* methods have been developed as non-animal alternatives. Read-across as an *in silico* tool interpolates the endpoint value for the compound of interest from respective experimental information of similar substances. It is considered to have a strong potential for providing confident predictions.

A fully automated read-across model for predicting the acute fish toxicity in terms of log LC_{50} has been developed and published. It employs atom-centred fragments (ACFs) to assess similarity between chemicals. Within OSIRIS, ACFs have already been used successfully to characterise the chemical domain of QSAR models. Basically, the ACF technology decomposes the molecular structure into units built from non-hydrogen atoms, associated with neighbour atoms. A similarity measure than is obtained from the comparison of the number of ACFs occurring in both compounds. The suggested read-across approach applies first-order and second-order ACFs with respect to the path length.

Experimental data of the 96-h fish toxicity (LC_{50}) towards fathead minnow (*Pimephales promelas*) for 692 organic chemicals were taken from literature, covering almost 9 orders of magnitude. The narcosis -level toxicity (baseline) can be predicted from the octanol/water partition coefficient by a simple log-linear regression model. The logarithmic toxicity enhancement *Te* then is obtained as the difference between the calculated baseline toxicity and the experimentally observed toxicity, both in logarithmic terms again. The proposed read-across approach predicts the logarithmic toxicity enhancement. The log LC_{50} prediction then can be obtained by combining the log *Te* from read-across with the baseline toxicity estimation through the octanol/ water partition coefficient.



Plot of the leave-one-out predictions for log LC_{50} (96-h toxicity towards fathead minnow) vs. the experimental values, with respect to different similarity threshold restrictions (brown = screening level confidence, orange = intermediate, green = high).

Depending on developed default values for the minimum similarity required for a chemical to qualify as read-across basis, log *Te* and log LC_{50} predictions can be obtained with screening-level, intermediate and good confidence. Since, due to the limited number of data, there was no external test set available, the model development together with respective statistical tests was carried out by a leave-one-out procedure. Reasonable similarity thresholds for the first-order ACFs differing for the screening level (no threshold at all), the intermediate level, and the high level confidence were obtained, as well as general threshold for the second-order ACFs, and respective weights to combine the first-order and second-order results. The Figure shows the comparison of predicted and experimental LC_{50} when applying the different similarity thresholds, taking the result from the highest possible level for each compound.

For the screening level, results could be obtained for all compounds. There was a predictive squared coefficient q^2 of 0.72 and a root-mean square error *rms* of 0.73 in logarithmic units. For the intermediate

OSIRIS Results Highlights

level, the number of results reduces to 419, but the performance increases to q^2 of 0.76 and *rms* of 0.60.

With the highest level of confidence, only results for 230 chemicals were possible. However, they yield q^2 of 0.87 and *rms* of 0.39.

A more detailed evaluation was performed by considering the log *Te* span width of the reference compounds. It could be shown that the more their log *Te* varied, the less confident their similarity-weighted average taken as the prediction result was.

Another important conclusion could be drawn by comparing the read-across results to the outcome of the ECOSAR models. For all three similarity thresholds, there is no intercorrelation between prediction errors of the read-across approach and ECOSAR. In a consensus modelling approach, the new read-across model and ECOSAR thus can be used together as complementary tools. The degree of agreement between both model predictions then provides additional confidence information that is not available from investigations of the individual model performances.

Additional information: Schüürmann G, Ebert R-U, Kühne R 2011. Quantitative read-across for predicting the acute fish toxicity of organic compounds. Environ. Sci. Technol. 45: 4616-4622

New OSIRIS Publications

Publications in Peer Reviewed Scientific Journals

- Jaworska J, Hoffmann S 2010. Integrated Testing Strategy (ITS) – Opportunities to better use existing data and guide future testing in toxicology. Altex 4: 231–242
- Engraff M, Solere C, Smith KEC, Mayer P, Dahllöf I 2011. Aquatic toxicity of PAHs and PAH mixtures at saturation to benthic amphipods: linking toxic effects to chemical activity. Aquatic Toxicology 102 (3-4): 142–149
- Undeman E, Czub G, McLachlan MS 2011. Modelling bioaccumulation in humans using poly-parameter linear free energy relationships (ppLFERs). Science of the Total Environment 409: 1726–1731
- Von der Ohe PC, Dulio V, De Deckere E, Slobodnik J, Kühne R, Ebert R-U, Schüürmann G, Brack W 2011. A new risk assessment approach for the prioritization of 500 classical and emerging organic microcontaminants as potential river basin specific pollutants under the European Water Framework Directive. Sci. Total Environ. 409: 2064–2077.
- Rallo R, France B, Liu R, Nair S, George S, Damoiseaux R, Giralt F, Nel A, Bradley K, Cohen Y 2011. Self-organizing map analysis of toxicity-related cell signaling pathways for metal and metal oxide nanoparticles. Environ. Sci. Technol. 45: 1695–1702
- Liu R, Rallo R, George S, Ji Z, Nair S, Nel AE, Cohen Y 2011. Classification NanoSAR development for cytotoxicity of metal oxide nanoparticles. small 7 (8): 1118–1126
- Toropova AP, Toropov AA, Benfenati E, Gini G 2011. Co-evolutions of correlations for QSAR of toxicity of organometallic and inorganic substances: An unexpected good prediction based on a model that seems untrustworthy. Chemometrics Intelligent Laboratory System 105 (2): 215–219
- Toropova AP, Toropov AA, Gonella Diaza R, Benfenati E, Gini G 2011. Analysis of the co-evolutions of correlations as a tool for QSAR-modeling of carcinogenicity: an unexpected good prediction based on a model that seems untrustworthy. Cent. Eur. J. Chem. 2011 (9) : 165–174

New OSIRIS Publications

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- Toropov AA, Toropova AP, Benfenati E, Gini G, Leszczynska D, Leszczynski J 2012. SMILES-based QSAR Approaches for Carcinogenicity and Anticancer Activity: Comparison of Correlation Weights for Identical SMILES Attributes. Anti-Cancer Agents in Medicinal Chemistry, in press, available online

The complete publication list with **links to the articles** is available at

www.osiris-reach.eu > Publications

Final OSIRIS Meeting and Final Stakeholder Workshop in Leipzig

The **Final OSIRIS General Assembly Meeting** was held **on 27 – 28 September 2011 in Leipzig, Germany** at the Helmholtz Centre for Environmental Research – UFZ, hosted by the OSIRIS Coordinator UFZ.

Delegates from the OSIRIS partners met for a final discussion of the project results.

On **29 September 2011**, the **Final OSIRIS Stakeholder Meeting** took place in the same location as final dissemination event.

The final version of the OSIRIS Integrated Testing Strategies (ITS) Webtool was demonstrated to Stakeholders.

The methods and Integrated Testing Strategies developed within OSIRIS for the different human health and environmental endpoints are implemented in the **web-based OSIRIS Tool**, which is publicly available with the end of the project and available at:

http://osiris.simpple.com/OSIRIS-ITS

Photos: Andrea Richarz

The OSIRIS Webtool includes ITS for:

- Skin sensitisation
- Repeated dose toxicity
- Mutagenicity & carcinogenicity
- Bioconcentration factor
- Aquatic toxicity.

The OSIRIS Webtool indicates what tests (If any) should be perfomed inorder to satisfy REACH data requirements.

OSIRIS Methods and Models Developed

OSIRIS developments include:

Screening methods

- Cut-off criteria for substance-specific waiving of BCF studies
- Screening method for persistent transformation products
- PBT (persistent, bioaccumulative, toxic) index model
- CMR (carcinogenic, mutagenic, reprotoxic) screening tool

Waiving opportunities

- Exposure-based waiving (environment, workers, consumers)
- TTC approach for inhalation and dermal exposure
- TTC values for drinking water

Models for toxicity prediction

- Experimental and computational determination of toxicity-related electrophilicity of chemicals (chemoassays, bioassays, quantum chemistry)
- Prediction of physico-chemical properties and toxicity from structure (ChemProp OSIRIS edition)
- Category formation and read-across approaches
- Prediction of internal exposure
- Prediction of aquatic hazard distribution (NOEC95)

Models for environmental exposure assessment

- Bioaccumulation of polar and non-polar compounds
- Fate of neutral and ionisable chemicals
- Fate of parent chemicals and their transformation products
- QSAR predictions of fate-related properties
- Probabilistic exposure assessment

Data collation

- OSIRIS-wide database system, implemented in ChemProp
- E-SovTox: online database on Russian (eco)toxicity data
- Toxicogenomics data

Data and model analysis

- Data quality assessment strategies
- Determination of the applicability domain

Optimisation possibilities of *in vitro* tests

- Passive dosing to control exposure concentrations

Optimisation possibilities of *in vivo* tests

- Guidance on the optimisation of *in vivo* tests
- Acute-chronic ratios to prioritise chemicals for chronic aquatic toxicity testing
- Data quality-related optimisation of testing protocols, *in vitro* and *in silico* approaches for ecotoxicity testing

Decision models

- Cost-effectiveness analysis model
- Value-of-Information model for sequential testing

ITS acceptance

- Survey on ITS implementation and acceptance

Public Software and Data from OSIRIS

An overview of available software developed with support from OSIRIS can be found at: http://www.osiris-reach.eu/index.php?en=22157, where short descriptions of the OSIRIS Webtool, ChemProp, ACC-HUMANsteady, DTU models, and E-SovTox are given.

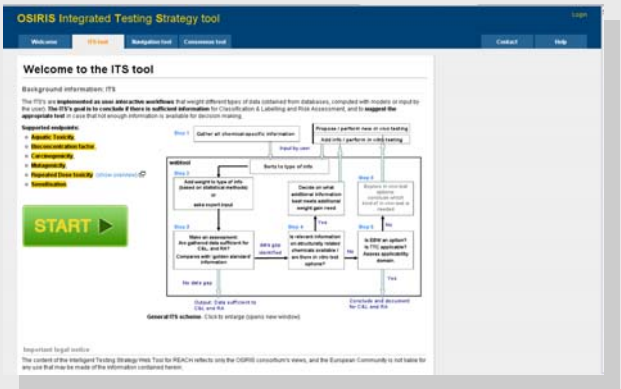
The OSIRIS Webtool

The OSIRIS ITS Webtool is freely accessible now. It is considered as the central software outcome of OSIRIS. The tool guides in performing ITS on

- skin sensitisation,
- repeated dose toxicity,
- mutagenicity, carcinogenicity,
- bioconcentration factor, and
- aquatic toxicity.

The direct link to the tool is: http://osiris.simpple.com/OSIRIS-ITS.

The use of the Webtool requires free registration at: http://osiris.simpple.com/OSIRIS-ITS/signUp.do.



ChemProp

The OSIRIS version of the local QSAR and chemical database system ChemProp is now freely available, based on a bilateral license agreement (one per working group) with partner UFZ. ChemProp contains a large number of prediction models for compound properties and endpoints. It is the official supplier of the data sets compiled from several partners within OSIRIS. This includes all data from the former partner project CAESAR.

Furthermore, the OSIRIS ITS Webtool can exploit ChemProp to retrieve knowledge on substructures and QSAR results. More information and the license file for download is available at http://www.ufz.de/index.php?en=6738.

ACC-HUMANsteady

ACC-HUMANsteady is a steady state (fugacity based) model of the bioaccumulation of organic contaminants, developed by partner SU. It is implemented as Excel spreadsheet and can be directly downloaded from the OSIRIS software webpage.

DTU Exposure Models

Several models developed by partner DTU are available as Excel files from http://homepage.env.dtu.dk/stt/Homepage%20anf/Website.htm:

- *K*oc models,
- the Multimedia Activity Model for Ionics MAMI, and
- the simulation model for ionic compounds in wastewater treatment plants, Activity SimpleTreat

and from http://homepage.env.dtu.dk/stt:

- plants uptake models and
- bioaccumulation models of ionic compounds.

E-SovTox

E-SovTox (partner NICPB) is a database with information from main publicly available sources of toxicity data published in Russian language. Access to E-SovTox will be given by the administrator after agreement of the potential user with the "Terms of use" and filling the online application form at : http://kbfi-databases.eu/.

OSIRIS Brochure

A brochure highlighting major OSIRIS results, especially the OSIRIS ITS Webtool, has been published and is available, along with the OSIRIS flyer summarising the OSIRIS methods and tools developed, as pdf-file on the OSIRIS website www.osiris-reach.eu.

Requests for the printed version can be addressed to osiris@ufz.de.

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OSIRIS is a EU 6th Framework Integrated Project, contract no. GOCE-CT-2007-037017.

SIXTH FRAMEWORK PROGRAMME