OSIRIS Newsletter

No. 6 April 2010

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Photo: Andrea Richards

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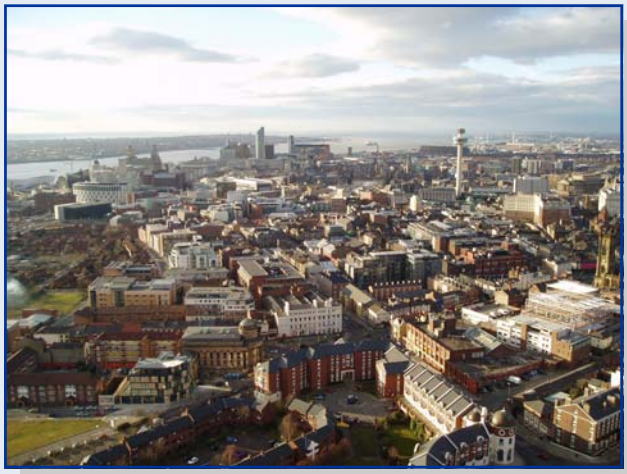
Third OSIRIS Annual Meeting

9—11 March 2010 • Liverpool, England

Photo: Sebastian Strempel

Third OSIRIS Annual Meeting



Meeting in Liverpool City Centre

The Third OSIRIS Annual Meeting took place on 9–11 March 2010 in Liverpool, England, hosted by OSIRIS partner Liverpool John Moores University.

65 participants from 14 countries and 30 OSIRIS partner institutions, as well as from the Advisory Board, met to discuss the results of the third year of the project and to plan future work.

As is appropriate for an English meeting, this report starts with the weather: considering that it has been snowing in Spain at the time of the meeting, it was fortunate for all participants that this year's OSIRIS meeting was held in spring-like Liverpool.

Results from the 3rd Year of the Project

The work packages within the five Research Pillars — Chemical Domain, Biological Domain, Exposure, Integration Strategies and Tools and Case Studies — presented their major results and ongoing activities. These included amongst others:

In **Pillar 1**, a cross-cutting activity on data quality assessment within (and beyond) OSIRIS, involving 21 authors from 12 partner institutions, contributed to the discussion on data quality from different (inter)disciplinary perspectives. Refined structure and property profile screening criteria for substances of concern and waiving of bioassays have been developed. New features have been included in the QSAR and database modules of the OSIRIS edition of the ChemProp software.

Confounding effects on soil biodegradation kinetics were investigated. Experimental and computational methods to quantify electrophilic reactivity and bioassay derived structural alerts for excess toxicity were developed.

An updated method to assess the applicability domain accounting for non-correctly predicted training chemicals, as well as atom-centred fragment based chemical domain categories, were presented.

In **Pillar 2**, the mammalian toxicity database has been extended further to include data on *in vivo* micronucleus mutagenicity results (ISSMIC) as well as a web-based database with toxicity data made available from Russian language sources (E-Sovtox). Threshold of Toxicological Concern (TTC) values for inhalation and oral exposure have been derived or refined.

The possibilities to optimise toxicity and ecotoxicity *in vivo* testing strategies (without performing *in vivo* testing) have been investigated. For example, *in vitro* and *in silico* approaches to predict bioconcentration factor (BCF) have been explored. The applicability of acute-chronic ratios of fish toxicity data as a tool to prioritise chemicals for chronic testing was analysed.

The acute toxicity of four anilines was tested in an inter-species context using different alternative cell and organism based assays. Toxicogenomics gene expression profiling has been used to determine differences in biological mechanisms.

Photos: Andrea Richarz, Sebastian Strempel.

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In **Pillar 3**, an uncertainty analysis has been performed for the models developed: a bioaccumulation model, a multimedia activity model for ionisable chemicals and a model for parent compounds and degradation products. Furthermore, the models were compared with existing models, e.g. EUSES. The results obtained will be used to make recommendations for the improvement and extension of the applicability domain of the EUSES bioaccumulation model.

A decision tree for exposure-based waiving (EBW), including worker and consumer exposure, has been developed. Exposure models and their possible use for EBW where further reviewed, including the new Advanced REACH tool (ART).

Models for pulmonary, gastrointestinal and dermal absorption have been developed, and integrated with a model for distribution and elimination. Physiologically based pharmacokinetic (PBPK) modelling is aimed at predicting human internal exposure.

In **Pillar 4**, the assumptions made in the cost-effectiveness analysis model and the direct costs for testing and non-testing data generation were evaluated. A questionnaire to examine Integrated Testing Strategies (ITS) implementation and acceptance was drafted.

The concepts and ITS frameworks developed for a categorical endpoint (skin sensitisation) and a continuous endpoint (repeated dose toxicity) were presented. A scheme for inclusion of EBW/TTC in a continuous endpoint ITS was developed.

Building blocks within the ITS for the assessment of aquatic toxicity were identified. *In silico* and *in vitro* methods as well as the possibility to waive testing are integrated in the scheme developed. The prototype of the chemical and biological Space Navigation Tool has been integrated into the ITS web tool.

The newest version of the OSIRIS web tool also includes the consensus tool developed within OSIRIS and supports two more endpoints (aquatic toxicity and skin sensitisation) in addition to the preliminary ITS for bioconcentration and mutagenicity already included.

In **Pillar 5**, the combined PBT (persistent, bioaccumulative, toxic) index developed was applied to a set of about 113,000 chemicals, and studies towards a mechanistic understanding of factors leading to PBT properties have been performed.

The reliability, relevance and applicability domain of *in vitro* methods and (Q)SAR models for skin and eye irritation inventoried previously have been explored.

Data on costs and animal use of tests for a "traditional" risk assessment of 10 potential drinking water contaminants were gathered as basis for the comparison with alternative risk assessment tools. Category formation and read-across approaches have been applied to these case study compounds.

Models for workplace exposure and for dermal uptake, as well as the ITS for skin sensitisation implemented in the OSIRIS web tool, have been evaluated.

Photos: Sebastian Strempel

Third OSIRIS Annual Meeting

Work package 6 reported on the Second OSIRIS Training course held in September 2009 in Milan, Italy, giving a theoretical background to risk assessment as well as practical software demonstrations. Planning for the next Training course (November 2010 in Milan) is advanced and it is expected that this will also be very well attended.

Stakeholder Feedback

The applications of the methods and models developed within OSIRIS for the REACH risk assessment process were discussed based on the reports of the discussions at the Third OSIRIS Stakeholder Workshop on 1-2 March 2010 in Berlin and the feedback received from Advisory Board members. The importance to integrate all models and methods developed within OSIRIS into practicable tools at the end of the project was stressed; recommendations for adaptations of the REACH Guidance documents will be useful. The acceptance by users and regulatory authorities is considered to be a crucial issue.

Photos: Sebastian Strempel, Andrea Richarz

Intra- and Inter-Pillar Discussions

Pillar break-out sessions allowed productive discussions within the Pillars of the results achieved and further planning of the work in OSIRIS.

The new objectives, deliverables and milestones set in the individual Pillars for the next, and last, 18 months of the project were presented to the consortium and interactions within and across work packages and Pillars were discussed intensively. Information needs across Pillars were identified and timelines set.

Inter-Pillar working groups had additional face-to-face meetings during the course of the annual meeting, and lively discussions came up during lunch and at the tea breaks.

A real English Gentlemen's Club

The conference dinner was organised at the historic Liverpool Athenaeum Club, a unique opportunity to see inside a traditional English "Gentlemen's Club". The meeting participants were received in the Newsroom and – after the sumptuous dinner – were invited to visit Liverpool's oldest library which is held within the Club.

… and more

Liverpool also had many other attractions to offer, the Beatles, of course, but also its cathedrals, museums and art galleries, the re-generated docks and last but not least numerous pubs to choose from. It has been reported that the most adventurous of the OSIRIS participants even went to climb mountains in Wales.

Third OSIRIS Stakeholder Workshop

In cooperation with the Federal Institute for Risk Assessment (BfR)

The Third OSIRIS Stakeholder Workshop was held on **1-2 March 2010** in cooperation with the Federal Institute for Risk Assessment in **Berlin, Germany**. Stakeholders from industry, regulatory authorities, NGOs and academia were invited to bring forward concerns and expectations and to discuss the applications of the findings of the research from OSIRIS in the REACH risk assessment process.

Non-testing Methods in OSIRIS

Mark Cronin, LJMU, gave an overview of risk assessment with non-testing methods in OSIRIS, focussing on *in silico* methods and tools, including QSARs, exposure models, databases, domain definition and category formation tools. These methods form the building blocks of the Integrated Testing Strategies (ITS) developed in the project.

Dinant Kroese, TNO, summarised the REACH context and explained the underlying concepts and weight of evidence (WoE) approaches for the ITS under development for different endpoints and their integration in the OSIRIS web tool.

Manfred Liebsch, ZEBET, reported on the validation of alternative testing strategies and stressed that validation of ITS is required but is difficult due to the expert judgement implicit in the strategies. Matthias Herzler, BfR, presented the BfR Decision Support System (DSS) to predict local effects as an example of a validated non-testing system.

Endpoint "Bioconcentration Factor"

Monika Nendza, AL, and Alessandra Roncaglioni, IRFMN, summarised the requirements of the endpoint within REACH, available BCF databases and estimation models and gave considerations on data quality and uncertainty. They presented chemistry-driven BCF modules (B/nonB classification model, QSARs) and the ITS integrated in the web tool.

Endpoint "Skin Sensitisation"

Andreas Luch, BfR, gave an overview of skin sensitisation testing in the frame of REACH and current developments in *in vitro* testing.

Mark Cronin reported on *in silico* approaches for predicting skin sensitisation, which overlap but differ in terms of number/type of data, mechanistic vs. non-mechanistic approaches, and modelling philosophy.

Joanna Jaworska, P&G, and Emiel Rorije, RIVM, presented Bayesian approaches to integrate different results. In the WoE approach, a defined REACH endpoint acts as golden standard to which alternative method performances are compared. Quality factors, e.g. Klimisch-like codes, are needed.

Group Discussions

Following the plenary presentations, the workshop participants discussed specific questions related to the two endpoints in small groups, for example how to define the limits of the applicability domain for the BCF model or the regulatory approach to uncertainty. The feedback received is being taken into account in the ongoing ITS development in OSIRIS.

Toxicity Testing in the 21st Century

To stimulate further discussions after dinner, Daniel Krewski, University of Ottawa, presented the vision of 21st century toxicity testing and the related current debate in the scientific and stakeholder community.

Photos: Christina Benghiat, Andrea Richarz

A detailed report will be made available through the OSIRIS website **www.osiris-reach.eu**.

Results of the OSIRIS Workshop on Mechanisms and Modes of Toxic Action

Photo: Mark Hewitt

A full report has been published in **ATLA** as part of a special edition on *in silico* techniques edited by Mark Cronin, Liverpool John Moores University on an influential **OSIRIS Workshop** that has made recommendations for the **use of toxicological mode and mechanism of action information to support informed hazard assessment**:

Vonk JA, Benigni R, Hewitt M, Nendza M, Segner H, van de Meent D, Cronin MTD 2009. The use of mechanisms and modes of toxic action in integrated testing strategies: the report and recommendations of a workshop held as part of the European Union OSIRIS Integrated Project. *Alternatives to Laboratory Animals* 37: 557–571.

The Workshop was held in Liverpool, England on 30 October 2008, being attended by over 35 delegates including experts from OSIRIS and key invited external leaders in the field. The aim of the Workshop was to build upon recent progress in this area from the US EPA, the International Programme for Chemical Safety (IPCS) and other groups.

The delegates first set about **defining the terms mode and mechanism of action**. A clear and obvious problem here is that researchers from different backgrounds (e.g. human health vs environmental) attached different meanings to these terms. It was agreed that rather loose definitions are required; it is the context of using this information that is more important. Delegates then split into three groups to discuss the role of modes and mechanisms of action for environmental toxicity, local human effects and chronic human toxicity.

The findings of the workshop clearly shape the state of the art into a usable form. There was overwhelming agreement that if information on modes and mechanisms of action can be captured, then it can be used to group chemicals into pragmatic categories. For instance, for **environmental toxicity**, the role of mechanistically based computational models for acute toxicity is well established – a key factor is whether a compound can be classified as being narcotic. This goes beyond acute toxicity, as the workshop concluded that **acute-chronic ratios** could be better applied within a mechanistic framework, i.e. the extrapolation is more reliable for narcotics. There are a number of methods of assigning mechanisms of action (e.g. the Verhaar rules) which are being developed and implemented in the OSIRIS project.

ATLA 37, 557–571, 2009 557

The Use of Mechanisms and Modes of Toxic Action in Integrated Testing Strategies: The Report and Recommendations of a Workshop held as part of the European Union OSIRIS Integrated Project

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For **human health effects**, the Workshop focussed on skin sensitisation (a local effect) and carcinogenicity. There is extensive mechanistic understanding of both endpoints. For the important REACH endpoint **skin sensitisation**, the immunological pathway leading to a response has been well established. The focus of modes and mechanisms of action is to capture knowledge on electrophilic chemistry which is the initiating event. This can be used as a direct predictor of toxicity or a method to group chemicals together. For **carcinogenicity**, consideration was given to genotoxic and non-genotoxic mechanisms. Genotoxic mechanisms can be captured with structural fragments, such information is already implemented in OSIRIS. Non-genotoxic mechanisms are more complex to understand and are an area of further development. One way in which OSIRIS is supporting all these activities is in the development of **high quality databases** for these endpoints.

The Workshop was able to form a consensus on all aspects. This is summarised in the report which describes the key knowledge on how to **group chemicals on a mechanistic basis**. This includes the state of the art of the techniques to achieve this. Many of these are implemented in, and will guide, the **OSIRIS Integrated Testing Strategies** and will make progress in the reduction of the use of animals for toxicological assessment.

A reprint of the paper is available from Mark Cronin (m.t.cronin@ljmu.ac.uk).

OSIRIS Results Highlights

Biodegradation database modelling (Partner CNRS)

CNRS, Environmental Microbial Genomics Group, Laboratoire Ampère, Lyon, France

The French partner CNRS has provided a **database** of **compound half-lives in different soils** under different conditions. This database is composed of data from a wide range of sources.

Preliminary attempts have been made to draw some initial conclusions about the **variables** that are important in **describing compound biodegradation half-lives**. The statistical analysis used here was simply multiple linear regression (MLR) by the method of least squares. The half-life of chemical compounds was represented as a mathematical function of their physico-chemical parameters or fragments and by soil characteristics:

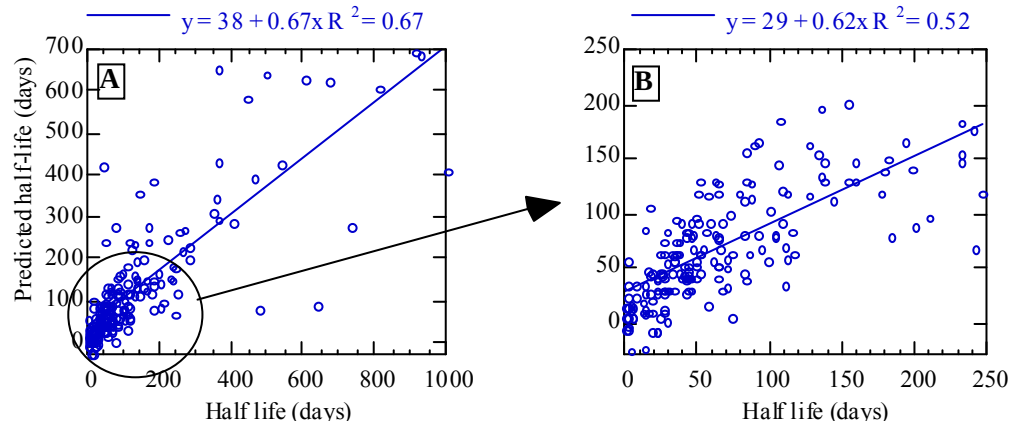
$$t_{1/2}=C_0 + C_1X_1 + C_2X_2 + \ldots C_nX_n$$

where X_n is a physico-chemical parameter or fragment or soil descriptor.

MLR was used to determine the values of the coefficients and constants C_n for any chosen combination of n compounds or combination of parameters which minimise the variance between the data and the model. The overall fit of the equation to the given data is expressed by the coefficient of determination r^2 normalised to the number of variables (adjusted r^2).

The conceptual model incorporates both **chemical and environmental parameters**. From this very heterogeneous database containing 244 data, multivariate regressions were performed to examine potential relationships between compound environmental half-life and molecule and soil characteristics together.

Although this preliminary correlation provides some insight into which molecular and soil characteristics were most pertinent, the lack of biological information concerning the number and capabilities of the soil microbiota limits our ability to cross-correlate different soils. In the ongoing soil testing by the partners ECT and CNRS, the variation due to soil type (and thus the number and activity of the soil microbiota) appeared to be the most critical to experimental reproducibility.



Chemical domain of QSAR models from Atom-Centred Fragments (Partner UFZ)

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

The knowledge of the **applicability domain** is crucial to correctly apply qualitative or quantitative structure-activity relationship (**QSAR**) models, as pointed out in the OECD guidelines for QSAR model validation. The applicability domain comprises the chemical space, the biological domain, etc. If a test compound is outside the chemical domain, the model reliability decreases, and the probability to obtain wrong estimations increases.

Regarding the **chemical space**, several aspects have to be taken into account, e.g. the physico-chemical domain, structural features, mechanistic aspects and also the metabolic domain in case that biotransformation is involved. Key properties affecting the bioavailability such as water solubility and partition coefficients of the compound of interest, as well as all descriptors applied, should not be outside the range of the corresponding properties in the model training set.

To address the structural aspects of the chemical

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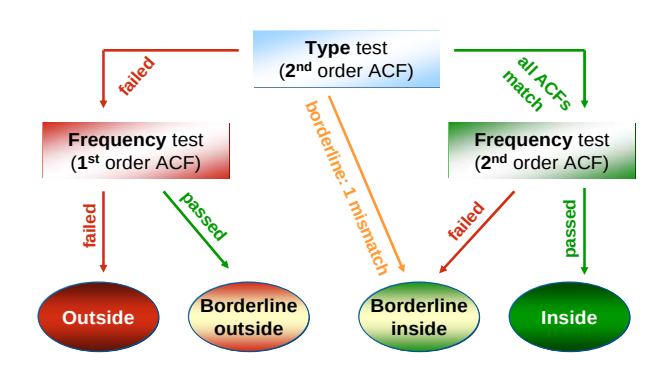
domain, atom types, structural complexity, and polarity may be considered. So far there is no generally accepted approach to define the chemical space of QSAR models. We have suggested a new technique to characterise the **structural domain** of compound sets based on the **atom-centred fragments** (ACF) concept. Molecules are subdivided into structural fragments consisting of a central atom and bonding neighbours. An ACF is defined through the atom type and the number and type of bound neighbours, and the respective bond types. The usefulness of this approach to locally correct estimation errors, to select appropriate models, and for a semi-quantitative *k*NN (*k* nearest neighbours) read-across model has already been shown by our group.

While some ACF applications with regard to the model domain already exist in the literature, there has been no detailed guidance and in particular no optimised procedure available to achieve this yet. Employing several data sets for continuous and categorical models, a new approach has been developed to **characterise the chemical domain based on ACFs** with path lengths of one and two bond lengths, i.e., for each atom considering its next



neighbour atoms and their neighbours. A criterion is obtained to decide whether a prediction compound is within the chemical space of a QSAR model with respect to the training set. To further define the model space, **four categories** were determined: **inside**, **borderline inside**, **borderline outside**, and **outside** and illustrated with examples.

This new technique can be applied to any compound-related model developed or data set provided. In particular, all QSAR models developed in our group will contain respective checks. The method is already available in the OSIRIS edition of the ChemProp software.

Additional information: Kühne R, Ebert R-U, Schüürmann G 2009. Chemical domain of QSAR models from atom-centered fragments. J. Chem. Inf. Model. 49: 2660-2669

Across-species relationships and toxicogenomic approaches (Partners UA, UNEXE, UB, VU, NICPB, KWR)

University of Antwerp, Laboratory of Ecophysiology, Biochemistry & Toxicology, Belgium; University of Exeter, School of Biosciences, UK; University of Bern, Centre for Fish and Wildlife Health, Switzerland; Vrije Universiteit Amsterdam, Department of Animal Ecology, The Netherlands; National Institute of Chemical Physics and Biophysics, In vitro & ecotoxicology group, Tallinn, Estonia; KWR, Watercycle Research Institute, Nieuwegein, The Netherlands

Mechanistic information is becoming a requirement for successful modelling and risk assessment and toxicogenomic techniques are promising techniques to elucidate the mode of action (MOA) of toxicants. The main objectives of research in work package 2.3 are to identify similarities and dissimilarities in response and MOA between toxicological model organisms after exposure to the test chemicals, to assess the power of **transcriptomics** in terms of unravelling MOAs and to assess the applicability of alternative assays. This will reduce the uncertainty due to differences in species susceptibility, and will allow to refine the risk assessment process. Furthermore, transcriptomics profiles provide insight in differences in MOA among similar and dissimilar compounds.

The **acute toxicity** of four case study compounds (aniline, 4-chloroaniline, 3,5-dichloroaniline and 2,3,4-trichloroaniline) was tested in an **interspecies context** using different alternative cell and organism based assays: neutral red cytotoxicity assay with the EPC cell line of *Cyprinus carpio*, luminescent bacteria test with *Aliivibrio fischeri* at 15°C and 20°C, bacterial growth inhibition test with *E. coli*, algae growth

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inhibition test with *Chlamydomonas reinhardtii*, algae growth inhibition test with *Pseudokirchneriella subcapitata*, immobilisation test with *Daphnia magna*, reproduction toxicity test with *Folsomia candida* and fish embryo toxicity tests with *Danio rerio* for 48h.

The obtained results indicate that the toxicity of the anilines depends on the degree of chlorosubstitution, i.e. structure of the chemicals, and also varies among the different test species. The general hypothesis of increasing toxicity with increasing chlorosubstitution was observed in all test systems except for *Daphnia magna* and *Folsomia candida* where an opposite response was seen.

The use of **mode of action**-based QSARs requires fundamental knowledge on the chemical as well as on the biological mechanisms of the compounds. The emphasis in MOA determinations, however, is too often based on chemical descriptors while biological descriptors are underrepresented. Consequently this can lead to MOA misclassification and wrong toxicity predictions. Biology-based alternatives for MOA prediction need to be considered.

Toxicogenomics is a promising technique to assess MOAs of chemicals. Different chemicals with different MOAs potentially give rise to different molecular fingerprints. The starting hypothesis is that compounds associated with similar mechanisms of toxicity yield similar gene expression profiles, which are distinct from profiles generated by other classes of chemicals. This means that chemicals from the same chemical category are likely to share a similar molecular fingerprint. It is hypothesised that by identifying "key genes or key clusters of genes", chemicals can be categorised.

The biological MOA of the four test compounds were tested. In order to test the power of transcriptomics, (dis)similarities in toxic biological MOAs were identified. Gene expression analyses were performed in rainbow trout cell line, RTL-W1, *Danio rerio* embryo, *Folsomia candida*, *E. coli*, *Chlamydomonas reinhardtii* and *Daphnia magna*. In addition, the Ames II mutagenicity test has been carried out for species comparison. The gene expression data were used to support and explain toxicity effects that were observed at higher levels of biological organisation. These data will be used to assess the **potential of biological descriptors** in compound classification and class prediction.

Model development for internal exposure (Partners CYPROTEX, TNO)

Cyprotex Discovery Ltd, Macclesfield, UK ; TNO Quality of Life, Zeist, The Netherlands

Prediction of human internal exposure to chemicals arising from external exposure is performed by means of a **physiologically based pharmacokinetic** (PBPK) model. For this purpose, models including mathematical descriptions of the physiological processes in the body are developed for the simulation of **absorption, distribution, metabolism and elimination** (ADME) of compounds in both rats and humans.

The models are developed to predict internal exposure after absorption via oral, dermal or inhalative exposure to REACH compounds, or following intravenous injection, and are designed to predict the internal exposure in rats and for humans. The similarity of the underlying models for rat and human enables the predictions for rat to be used as a surrogate for predictions for human exposure – necessary because of the difficulty of obtaining good quality datasets for human exposure for REACH-relevant compounds.

In general, the compound-specific information for these chemicals is limited as compared to the pharmaceuticals compounds for which originally physiologically based models are designed. Therefore, a **generic kinetic model** (i.e. a model that can be applied to a wide range of compounds, rather than one, or a few related compounds) is designed and where needed compound-specific information is either measured *in vitro* or predicted using QSARs. A third option is to use default values for certain parameters for which no measured or predicted values are available.

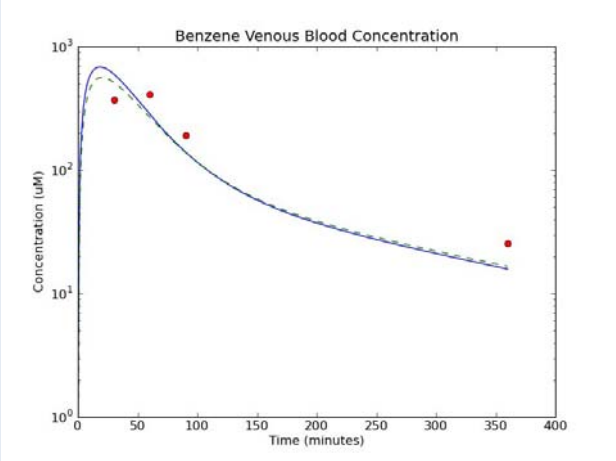
A **preliminary validation** of the PBPK models developed has been carried out. Predictions have been performed for seven compounds, introduced via one or more routes (oral, pulmonary, dermal and/or intravenous injection) in human or rats, and compared to existing *in vivo* data.

OSIRIS Results Highlights

The preliminary investigation of the utility of generic PBPK models for the **prediction of toxicokinetics** (TK) **of REACH-relevant compounds** has illustrated that reasonable predictions are achievable.

For the purposes of OSIRIS, it is planned that TK prediction will be incorporated into **exposure-based waiving** for the **Integrated Testing Strategies** (ITS) developed for human health end-points. The key TK parameters of amount absorbed (for oral, pulmonary and dermal exposure routes) and half-life will be predicted. Consequently, further validation of the models' utility for incorporation in ITS will focus on the reliability of predicting (1) **amount absorbed** and (2) **half-life**.

Particular attention will be paid to the **chemical domain** within which the predictions are expected to be valid. For half-life, this requires particular attention to be paid to determining whether or not all means of elimination have been identified. It also requires that chemistry-specific tissue binding over and above that which can be predicted from generic partitioning can be accounted for within the ITS.



Predicted and observed blood concentrations for oral administration of benzene to adult male Wistar rats. Red circles: measured *in vivo* concentrations; blue solid line: predicted concentration in the bulk venous plasma; green dashed line: predicted concentration at the sample site.

Additional information: Metcalfe PD, Thomas S 2010. Challenges in the prediction and modelling of oral absorption and bioavailability. Curr. Opinion Drug Disc. Devel. 13: 104-110

Formation of categories for read-across of endpoints relating to reproductive toxicity (Partner LJMU)

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

A recent paper has illustrated the use of category formation and read-across to predict endpoints relevant to reproductive toxicity – one of the major endpoints for REACH. **Category formation** is one of the key *in silico* methods being developed in the OSIRIS project. This technique is one of the most applicable methods to make **predictions of complex human health endpoints.** Once a robust category has been formed i.e. a grouping of chemicals that are related on some rational basis, toxicological data can be found, interpolation or read-across can be performed to make predictions.

The OSIRIS project is developing many **approaches** to form categories to predict toxicity. Amongst these, those **based on modes and mechanisms of toxic action** are preferred (see report on the related OSIRIS workshop on p. 6). However, these approaches are applicable only if a mode or mechanism is known. For complex endpoints, such as reproductive toxicity, information on modes and mechanisms is often lacking. Therefore, a novel approach applied in the OSIRIS project has been to use **2D measures of molecular similarity** to form categories.

The freely available Toxmatch software, developed by the European Commission's Joint Research Centre (JRC — an OSIRIS partner), Ispra, Italy was applied to form categories of molecules. To illustrate its use, a **data set of teratogencity values** for chemicals with many different (and mostly unknown) mechanisms was investigated. Categories of structurally similar chemicals were created which allowed for read-across to make predictions for compounds excluded from the training set i.e. a true estimation of predictivity. It was concluded that 2D similarity methods offer a useful method for building

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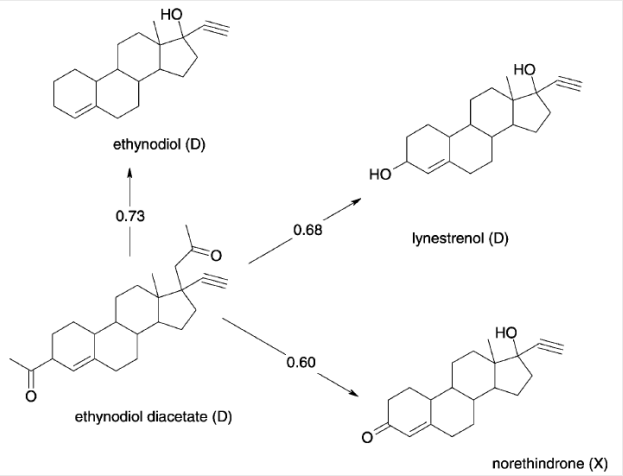
chemical categories for teratogenicity in which *a priori* mechanistic knowledge is limited. The study has provided a valuable insight into strategies to create "similarity-based" categories and use them to make read-across predictions of toxicity for complex human health endpoints.

A simple example of such a category (the numbers are the level of similarity) is shown in the figure. The consensus from the read-across within this category is the correct prediction of the query chemical (ethynodiol diacetate) to be teratogenic.



Additional information: Enoch SJ, Cronin MTD, Madden JC, Hewitt M 2009. Formation of structural categories to allow for read-across for teratogenicity. QSAR and Combinatorial Science 28: 696-708

ITS implementation and acceptance

OSIRIS Stakeholder interviews

The **comprehensive data requirements** as well as the **animal welfare concerns** put forward by REACH require a "paradigm shift" of the current risk assessment from an extensive hazard testing to a risk-driven approach. In this context, Intelligent or **Integrated Testing Strategies** (ITSs), taking into account testing and non-testing information as well as exposure information, have been considered appropriate tools for more efficient and flexible toxicity testing. In particular, ITSs are expected to meet information requirements in a quicker and more efficient way (i.e. at lower costs and with less animal use) compared to standard tests.

However, the usefulness of ITSs for the REACH process depends on the actual use by stakeholders such as chemical industry, commercial laboratories, consultancies, research institutions, non-governmental organisations, and regulatory agencies on the national level, and on the **acceptance of the results** by ECHA. ITSs will only be used if they respond to the **users' needs**.

Little is known about the users' perspective on ITS implementation and acceptance. Therefore the OSIRIS project (Partners DIA and WUR) will **investigate stakeholders' views** by performing interviews with members from the different stakeholder groups to address:

- the definition of ITS
- the scope and limitations of ITSs use for hazard and risk assessment of chemicals in the context of REACH, including the valuation of animal welfare
- the challenges and requirements for ensuring or improving ITS acceptance and implementation.

As a first step, **qualitative interviews** will be carried out where interviewees are invited to express their views, opinions and experience. The interviews will be performed by telephone and will take approximately 30 minutes.

In a second step, based on the outcomes of these qualitative interviews, a **questionnaire** will be developed and distributed, addressing the general interview questions in more detail.

If you are interested in supporting this investigation on ITS acceptance, please contact:

Christina Benighaus (benighaus@dialogik-expert.de)
or
Silke Gabbert (silke.gabbert@wur.nl).

Obituary

In memoriam Henri-Charles Dubourguier 06.02.1948–11.03.2010

It is with deep sorrow that we have to inform you of the sudden passing of Henri-Charles Dubourguier after stubborn fight with lung cancer. Several of you inquired about his participation in the Liverpool meeting, missing the questions that he used to ask. As he always told himself in his characteristic French English: "I am a provocateur". Only a few days earlier he was working behind his desk here in Tallinn, encouraging his students. His last paper (H-C was a corresponding author) related to OSIRIS was submitted to ATLA on 1 March: A web-based database on main publicly available sources of toxicity data published in Russian language (co-authors M. Sihtmäe, I. Blinova, V. Aruoja, A. Kahru).

Henri-Charles Dubourguier was born in 1948. He graduated at the National Institute of Applied Sciences (France) as a biologist and biochemist in 1972. He obtained his PhD in biochemistry in 1977 (University of Clermont-Ferrand), the Diploma of Microbiology (1975) and the Diploma of Immunology (1976) at the Pasteur Institute of Paris. 1972–1981 he worked on neonatal bacterial and viral diseases in animals at INRA-Theix, where he invented several animal vaccines (French, European and US patents). 1981-1988 he worked at INRA-Lille on the microbiology of anaerobic ecosystems and its consequences for engineering of industrial scale anaerobic digesters. 1988-1993 he studied physiology and genetics of anaerobic bacteria at the University of Lille. Since 1993 he was involved in environmental research with industrial and public partners at the "Institut Supérieur d´Agriculture" of Lille, particularly on bioremediation and mobility of organic and inorganic pollutants in soils for the remediation of large former industrial polluted sites.

6 October 2009, Blejsko jezero, two days before the Pillar 2 meeting in Ljubljana.

Since 2000 his private and scientific life was related to Estonia. He moved to Estonia permanently in 2006 and started to work at NICPB and also at the Estonian University of Life Sciences.

His enthusiasm got him involved with OSIRIS where he introduced several novel aspects: his interests ranged from Russian toxicity databases (that he deciphered using the Google-translator!) to QSARs of substituted anilines and phenols.

Henri-Charles Dubourguier published more than 80 scientific papers and supervised 20 MSc and 17 PhD theses. He was supervising four PhD students at the time, including OSIRIS-involved Mariliis Sihtmäe and Villem Aruoja.

Not less important for the people around him was his role as the ambassador of French culture in Estonia, especially the science of food, wine and dancing. We envied him also for his ability to see and treasure the beauty of our country. He could be regarded even more Estonian than most Estonians.

Henri-Charles will be remembered as a close friend, colleague and a scholar. He will be sadly missed. According to his wish, his ashes will be buried in Estonia.

Anne Kahru, Mariliis Sithmäe, Villem Aruoja

New OSIRIS Publications

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

www.osiris-reach.eu
> OSIRIS Publications

Publications in Peer Reviewed Scientific Journals

- Kahru A, Dubourguier HC 2009. From ecotoxicology to nanoecotoxicology. Toxicology 269:105-119
- Kühne R, Ebert R-U, Schüürmann G 2009. Chemical domain of QSAR models from atom-centered fragments. J. Chem. Inf. Model. 49: 2660-2669
- Smith KEC, Oostingh GJ, Mayer P 2009. Passive dosing for producing defined and constant exposure of hydrophobic organic compounds during in vitro toxicity tests. Chem. Res. Toxicol. 23: 55-65

New OSIRIS Publications

- Vonk JA, Benigni R, Hewitt M, Nendza M, Segner H, van de Meent D, Cronin MTD 2009. The use of mechanisms and modes of toxic action in integrated testing strategies: the report and recommendations of a workshop held as part of the European Union OSIRIS Integrated Project. ATLA 37: 557–571
- Vandenbrouck T, Jones OAH, Dom N, Griffin JL, De Coen W 2010. Mixtures of similarly acting compounds in Daphnia magna: From gene to metabolite and beyond. Environment International 36: 254-268
- Birch H, Gouliarmou V, Lutzhoft HCH, Mikkelsen PS, Mayer P 2010. Passive dosing to determine the speciation of hydrophobic organic chemicals in aqueous samples. Anal. Chem. 82: 1142-1146
- Smith KEC, Dom N, Blust R, Mayer P 2010. Controlling and maintaining exposure of hydrophobic organic compounds in aquatic toxicity tests by passive dosing. Aquat. Toxicol., in press, available online
- Meinert C, Emma Schymanski E, Küster E, Kühne R, Schüürmann G, Brack W 2010. Application of preparative capillary gas chromatography (pcGC), automated structure generation and mutagenicity prediction to improve effect-directed analysis of genotoxicants in a contaminated groundwater. ESPR - Environ. Sci. & Pollut. Res. 17: 885-897
- Schriks M, Heringa MB, van der Kooi MME, de Voogt P, van Wezel AP 2010. Toxicological relevance of emerging contaminants for drinking water quality. Water Research 44(2), 461-476
- Hewitt M, Ellison CM, Enoch SJ, Madden JC, Cronin MTD 2009. Integrating (Q)SAR, expert system and read-across approaches for the prediction of developmental toxicity. Reproductive Toxicology, in press, available online
- Böhnhardt A, Kühne R, Ebert R-U, Schüürmann G 2010. Predicting rate constants of OH-mediated indirect photolysis - advances for oxygenated compounds through a molecular orbital HF/6-31G** approach. Theor. Chem. Acc., in press, available online
- Jaworska J, Gabbert S, Aldenberg T 2010. Towards optimization of chemical testing under REACH: A Bayesian network approach to Integrated Testing Strategies. Regul. Toxicol. Pharmacol., in press, available online

Third OSIRIS Training Course

The next OSIRIS Training Course will be held in **November 2010** at the **Mario Negri Institute** in **Milan, Italy**.

It will comprise both lectures on basic concepts underlying chemical safety assessment and the REACH regulatory framework as well as practical software and web tool demonstrations.

The training will cover several topics related to **risk assessment** and **Integrated Testing Strategies** (ITS) fit for REACH.

A special section of the course will be devoted to the **practical application of QSAR** (qualitative or quantitative structure-activity relationship) **and expert system tools** for predicting a human endpoint (mutagenicity / genotoxicity) and an environmental endpoint (bioconcentration factor). A number of case studies will be presented.

Details on the programme, venue and registration will be announced on the OSIRIS website **www.osiris-reach.eu**.

Conference Calendar: OSIRIS-related Events

Environmental Toxicology 2010 - Third International Conference on Environmental Toxicology
4 – 6 May 2010, Limassol, Cyprus
http://www.wessex.ac.uk/10-conferences/environmental-toxicology-2010.html

SETAC Europe 20th Annual Meeting
23 – 27 May 2010, Seville, Spain
http://seville.setac.eu

14th International Workshop on Quantitative Structure-Activity Relationships (QSARs) in Environmental Sciences
24 – 28 May 2010, Montreal, Canada
http://www.qsar2010-montreal.com/

ICCS 2010 - International Conference on Computational Science
31 May – 2 June 2010, Amsterdam, The Netherlands
http://www.iccs-meeting.org/

IUTOX-2010 - XII International Congress of Toxicology
11 – 15 July 2010, Barcelona, Spain
Spanish Association of Toxicology (AETOX)
EUROTOX in the name of the International Union of Toxicology (IUTOX)
http://gestion.pacifico-meetings.com/www/iutox2010/

Fifth International Conference on Environmental Science and Technology
12 – 16 July 2010, Houston, USA
http://www.aasci.org/conference/env/2010

Predictive ADMET Workshop
2 – 6 August 2010, Oxford, UK
Application of Predictive ADME and Toxicology methods to case studies, a Hands-on 5 Day eCheminfo Workshop Week
http://echeminfo.com/COMTY_oxfordadmet10

3rd EuCheMS Chemistry Congress
29 August – 2 September 2010, Nürnberg, Germany
European Association for Chemical and Molecular Sciences
http://www.euchems-congress2010.org/ecc.htm

16th Congress on Alternatives to Animal Testing – Linz 2010, 16th International Congress on In Vitro Toxicology – ESTIV 2010
2 – 4 September 2010, Linz, Austria
EUSAAT - European Society for Alternatives to Animal Testing, ESTIV - European Society of Toxicology in vitro, zet - Austrian Centre for Alternative and Complementary Methods to Animal Testing
http://www.eusaat.org/index.php/2010

Joint Meeting of the SETAC-GLB and GDCh
6 – 9 September 2010, Dessau, Germany
Society of Environmental Toxicology and Chemistry (SETAC GLB), German Chemical Society (GDCh)
http://www.gdch.de/vas/tagungen/tg/5414.htm

Risk Analysis 2010 - 7th International Conference on Computer Simulation in Risk Analysis and Hazard Mitigation
13 – 15 September 2010, Algarve, Portugal
http://www.wessex.ac.uk/10-conferences/risk-analysis-2010-3.html

18th European Symposium on Quantitative Structure-Activity Relationships
19 – 24 September 2010, Rhodes, Greece
http://www.euroqsar2010.gr/

2nd Lhasa Symposium on New Horizons in Toxicity Prediction
23 – 24 September 2010, Leeds, UK
http://www.lhasasymposium.com/

www.osiris-reach.eu > OSIRIS Events and Activities

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