OSIRIS Newsletter

No. 8 October 2010

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Photos: Andrea Richarz

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OSIRIS ITS Meeting & ITS Stakeholder Workshop

Delegates from several OSIRIS partner institutes will meet on **2–3 November 2010** at the Mario Negri Institute in **Milan, Italy**, to discuss the Integrated Testing Strategies (ITS) and OSIRIS Webtool under development (see pages 2-3) for the human health and environmental endpoints

- skin sensitisation
- mutagenicity & carcinogenicity
- repeated dose toxicity
- bioconcentration factor
- aquatic toxicity

in view of the upcoming major dissemination event:

The next **OSIRIS Stakeholder Workshop** is scheduled for **beginning of 2011**.

Key stakeholders and experts from regulatory authorities and industry will be invited to test the methods and ITS developed within OSIRIS – integrated in the OSIRIS Webtool – and to give feedback for the final phase of the project.

The OSIRIS ITS Webtool

Optimised strategies for the risk assessment of chemicals under REACH

According to the new European legislation on chemicals and their safe use REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) all industrial chemicals produced or imported in quantities above 1 tonne per year have to be **evaluated** regarding their **ecotoxicological and toxicological effects**. Considering the currently used testing schemes, this procedure will result in a significant increase in animal tests, contrary to the goal of REACH to **reduce animal testing** where possible.

The 31 OSIRIS partners from 14 countries – including 24 research institutes, 5 small and medium-sized enterprises and 2 manufacturers of chemicals and chemical products – work together on the development of **Integrated Testing Strategies** (ITS) considering both non-test and test information and thus combining different approaches for the evaluation of chemicals, in order to support the chemicals risk assessment under REACH and to reduce *in vivo* tests. The methods and ITS developed are implemented in the **webbased OSIRIS Tool**, which will be made publicly **available to end-users** from industry and regulatory authorities.

OSIRIS integrates a large variety of scientific disciplines such as biology, chemistry, toxicology, ecotoxicology, toxicogenomics, statistics, information science, decision theory, as well as social sciences and economy.

Integrated Testing Strategies

ITS shift risk assessment from a "box-ticking" approach with extensive animal testing to a more efficient, context-specific and substance-tailored approach. The underlying principle is to take advantage of **existing information** before experimental testing, to group information about **similar substances** and to integrate **exposure considerations**.

The OSIRIS ITS under development consider different alternative approaches and information sources and aim to contribute to

- reduce chemical testing to the extent needed
- increase the use of non-testing information for regulatory decisions
- obtain the same level of safety using less animal tests.

The framework envisaged in OSIRIS comprises **complementary approaches** such as

- chemical and biological read-across
- qualitative and quantitative structure-activity relationships (QSAR)
- *in vitro* test results
- (existing) *in vivo* test data
- chemoassays
- *omics*
- exposure considerations:
  Thresholds of Toxicological Concern (TTC)
  Exposure-Based Waiving (EBW)

The OSIRIS ITS Webtool also considers cost-effectiveness-analyses.

Endpoints in the OSIRIS Webtool

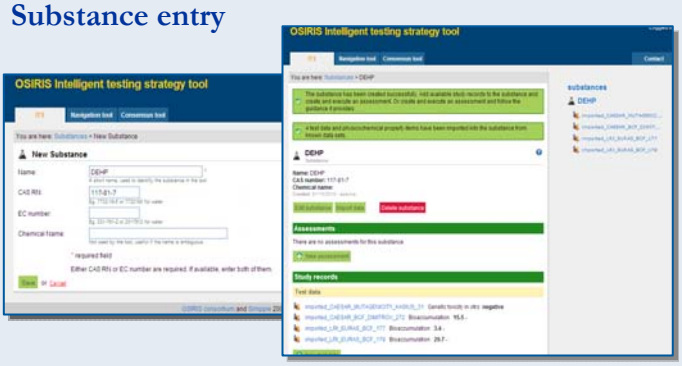
- Skin sensitisation
- Mutagenicity & carcinogenicity
- Repeated dose toxicity
- Bioconcentration factor
- Aquatic toxicity

The OSIRIS ITS Webtool

Functionalities of the OSIRIS Webtool

The different and possibly contradictory information is weighted and the respective uncertainties taken into account in a **Weight of Evidence** approach.

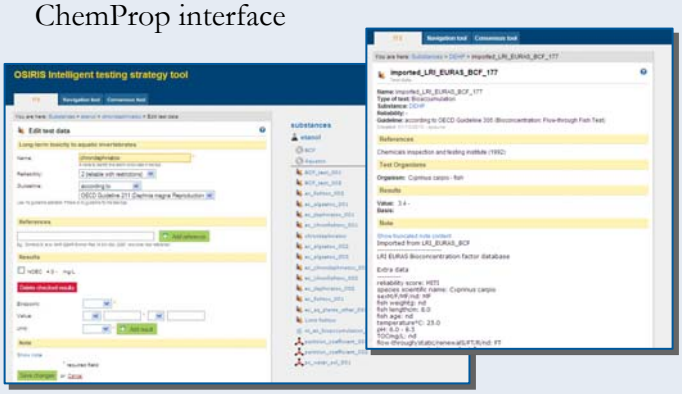
Substance entry



Data entry:

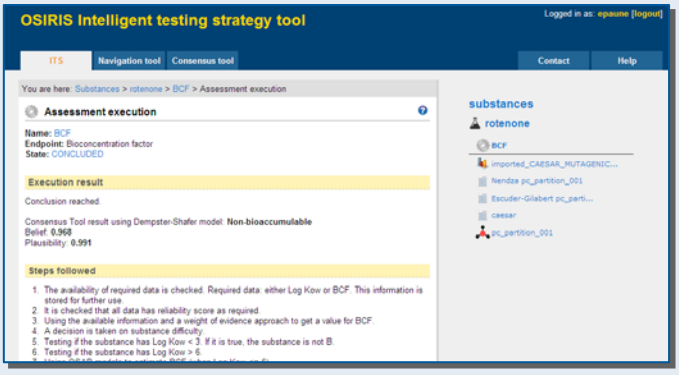
in vitro, in vivo test data,
in silico data,
physico-chemical properties

OSIRIS databases integrated through ChemProp interface

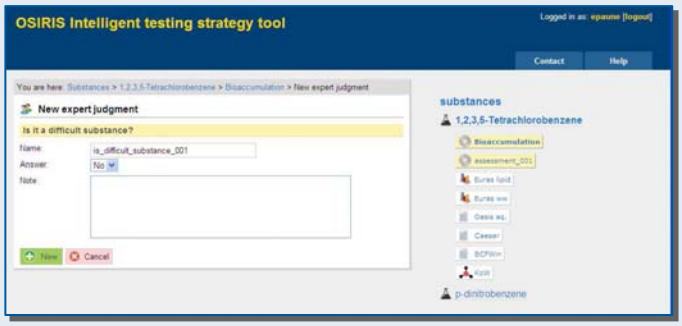


Assessment of information

according to endpoints and REACH requirements

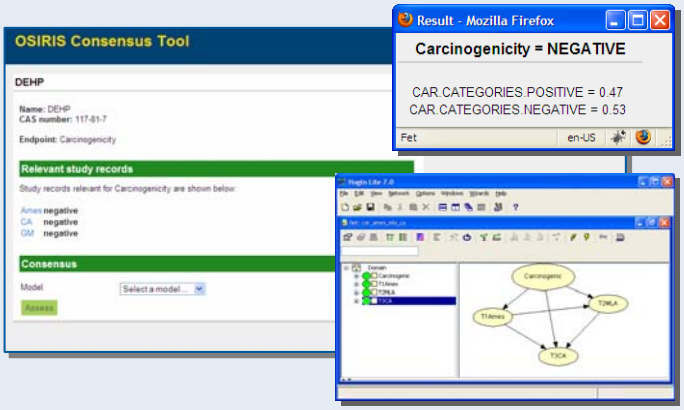


Expert judgement entry



Decision theory approaches:

Bayesian Networks (see issue No. 7) and Dempster-Shafer theory of evidence implemented in the **OSIRIS Consensus Tool** (see issue No. 4);
value-of-information approach (see issue No. 7)



Integrated **Chemical Space Navigation Tool** as visual aid for pre-screening tasks (see issue No. 3)

Result: The OSIRIS Webtool indicates what tests (if any) should be performed in order to satisfy REACH data requirements.
Data used and decisions taken are documented.

OSIRIS Results Highlights

Mutagenicity/genotoxicity testing strategies, a need to be updated (Partner ISS)

Istituto Superiore di Sanita, Department of Environment and Primary Prevention, Rome, Italy

It appears that strategies for genotoxicity / mutagenicity testing, both as **pre-screening of carcinogenicity** and as basis for **mutagenicity classification**, continue to be in the limelight, with increased interest.

The mechanistic findings that are still at the basis of the science and regulation of mutagens and carcinogens were established in the 1970's. Two independent lines of research were going on: a) research by the Millers pointing to the **carcinogenic properties of electrophilic chemicals**, potentially able to react with the DNA; b) research of mutagenists on the ability of chemicals to induce mutation, thus being potentially able to elicit heritable genetic damage. A highly productive cross-fertilisation between the two fields took place, with remarkable advantages for both. This gave rise to: a) the theory that electrophilic chemicals (per se, or after metabolic transformation) are able to induce both mutations and cancer; and b) the generation of **short-term mutagenicity (STT) assays** (e.g., the Salmonella typhimurium or Ames test, incorporating metabolic activation) for identifying mutagenic/genotoxic chemicals (hence potential carcinogens) (Zeiger 2004). Another important contribution came from John Ashby, that listed the chemical reactive groups present in carcinogens (**Structural Alerts**) (Ashby 1985).

Subsequently major research efforts focused on the hypothesis "mutation = cancer", and more than 100 STTs were developed, based on different genetic endpoints and types of cells, as to (hopefully) complement the Salmonella assay (Zeiger 2004).

Today it appears that the original hypothesis "mutation = cancer" is only valid within the limited area of the **DNA-reactive chemicals**: these induce cancer, together with a wide spectrum of mutations. For these chemicals, the best predictor of carcinogenicity is the Ames test. For the chemicals that are negative in Salmonella, but positive in other *in vitro* assays (e.g., clastogenicity) no correlation with, and predictive ability for carcinogenicity is apparent. Thus, no *in vitro*, mutagenicity-based STTs complementary to Salmonella are available today (Zeiger 1998, Benigni et al. 2010a).

Another working hypothesis was that *in vitro* positives should be confirmed through an *in vivo* genotoxicity assay; however it has been demonstrated that **existing *in vivo* tests are extremely insensitive** and give a majority of false negative results (Benigni et al. 2010b).

Overall, this evidence points to the need of re-thinking the entire mutagenicity/genotoxicity testing strategy as present in regulatory schemes. It should be emphasied that this is necessary not only for the use of STTs as pre-screening of carcinogenicity, but also for the mutagenicity classification itself. In fact, in spite of the formal separation between mutagenicity and carcinogenicity classifications in e.g., REACH, the reality is that, in practice, the **STTs in use**: a) can **only detect somatic mutation** and not heritable genetic damage; and b) were explicitly aimed at predicting, and calibrated so as to **match chemical carcinogenicity**.

Recently, we have analysed results relative to the Cell Transformation Assays (CTA). It appears that the Syrian Hamster Embryo (SHE) cell assay outperforms the other CTAs (BALB, C3H), and is sensitive to both DNA-reactive (genotoxic) and non-genotoxic carcinogens. For the prediction of carcinogens, a **tiered approach** consisting of: Step 1) Salmonella or Toxtree Structural Alerts; if negative, then Step 2) SHE, has demonstrated to reduce to only 10% the number of carcinogens in a sample of around 140 representative chemicals.

References

Ashby J 1985. Environ. Mutagen. 7: 919-921

Benigni R, Bossa C, Tcheremenskaia O, Giuliani A 2010a. Exp. Opin. Drug Metab. Toxicol. 6: 1-11

Benigni R, Bossa C, Worth A 2010b. Mutagenesis 25: 335-341

Zeiger E 1998. Regulat. Pharmacol. Toxicol. 28: 85-95

Zeiger E 2004. Environ. Health Perspect. 44: 363-371

OSIRIS Results Highlights

Exposure based waiving under REACH (Partners RIVM, TNO, FhG)

National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; TNO Quality of Life, Zeist, The Netherlands; Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany

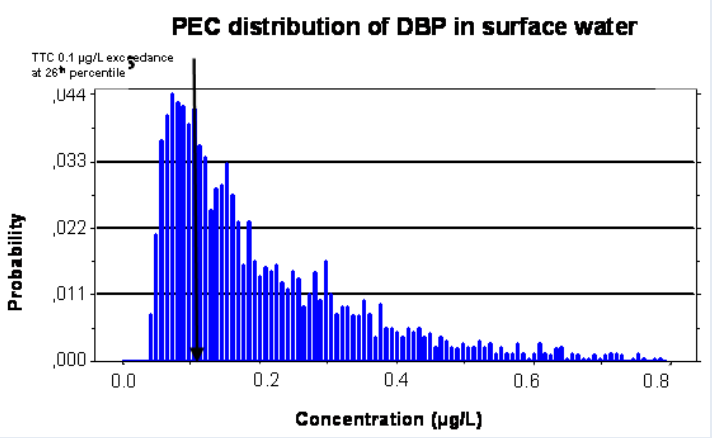
Within the REACH framework, but also within OECD, there is understanding that for reasons of animal welfare, costs and logistics, it is important to limit the number of tests to be conducted. **Exposure based waiving (EBW)** is a potentially important **element in alternative testing strategies**. In a recent publication, the criteria for exposure based waiving as foreseen in the REACH regulation have been described and more detail to the REACH requirements for exposure based waiving has been given.

The principle behind any EBW is that there are situations when human or environmental exposures are so low or infrequent that there is a very low probability that the acquisition of additional effect information may lead to an improvement in the ability to manage risk. EBW therefore is **risk based** and **needs thorough knowledge on exposure** as well as **on effects criteria**. Exposure models have been analysed and the uncertainty in their predictions has been discussed as well as no-effect criteria such as the Threshold of Toxicological Concern, termed **no-further-action level (NFAL).** Examples of EBW have been provided for environmental, consumer and worker exposure.

REACH only allows EBW in a limited number of cases with **constraints** on tonnage levels, types of tests to be waived and the need for a thorough **Exposure Scenario (ES)** and exposure assessment throughout the life cycle of a chemical and for all human exposure routes and environmental pathways. EBW will only be considered a real option by industry if a **cost-benefit analysis** shows an advantage, which may heavily depend on the weighing factor one applies for the non-use of experimental animals.

For many substances, Predicted No Effect Levels (PNECs) and Derived No Effect Levels (DNELs) will not be available as NFALs. For such data-poor substances the **concept of Threshold of Toxicological Concern** (TTC) has been proposed as a pragmatic approach to establish the exposure level below which no adverse effects on human health or an environment ecosystem are expected to occur. TTCs are derived for structural classes of substances by analysing the distribution of NOELs from *in vivo* studies. To apply the TTC concept, information about the chemical structure of the substance, but not toxicological information, is prerequisite.

The possible **application of EBW for aquatic toxicity tests** has been exemplified on the basis of the substance dibutylphthalate (DBP) using the EXCEL spreadsheet version of EUSES with the add-in Crystal Ball installed. The example concerns the production/formulation of adhesives including DBP with a total estimated tonnage level in the EU produced of 100 kg/annum. Corresponding emission characteristics and other used input distributions, i.e., physical and chemical properties (like water solubility and vapour pressure, etc.) and degradation and transformation rates (like degradation of DBP in surface water, air and sediment, etc.) were used and inserted into EUSES. By running EUSES with 2000 iterations (latin hypercube sampling) a Predicted Environmental Concentration (PEC) distribution of DBP in fresh water was derived as illustrated in the figure.



PEC-distribution of DBP in surface water.

OSIRIS Results Highlights

The figure illustrates the distribution (histogram and best fit overlay) of the simulated PECs in fresh waters. Assuming that the Threshold of No Concern for freshwater systems (ETNCaq) for organic chemicals of 0.1 µg/L is the best estimate representing a NFAL for surface water, it can be seen that the TTC level is exceeded at the 26th percentile of the PEC distribution. EBW would not be justifiable. However, if the PNEC of 10 µg/L for DBP from the EC Risk Assessment Report 2003 is used as NFAL, the PEC distribution is below this level and EBW is justifiable. Specific PNEC-values are to be preferred above generic TTCs.

Similar examples were developed for EBW-analyses for **consumer and worker exposure**.

More information is available in the full article: Vermeire T, van de Bovenkamp M, Bruinen de Bruin Y, Delmaar C, van Engelen J, Escher S, Marquart H, Meijster T 2010. Exposure based waiving under REACH. Regul. Toxicol. Pharmacol., in press, available online, DOI: 10.1016/j.yrtph.2010.08.007.

Overview of software models for genotoxicity (Partner JRC)

European Commission's Joint Research Centre, Institute for Health & Consumer Protection, Computational Toxicology Group, Ispra, Italy

Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material in cells or organisms. These changes may involve a single gene (point mutations), a block of genes or entire chromosomes (structural or numerical chromosome aberrations).
Genotoxicity is a broader term and refers to processes that alter the structure, information content or segregation of DNA and which are not necessarily associated with mutagenicity. Such processes include unscheduled DNA synthesis (UDS), sister chromatid exchange (SCE), DNA strandbreaks, DNA adduct formation, and mitotic recombination. In many cases, genotoxicity may lead to cancer. Thus, genotoxicity testing is performed to assess the potential of substances to induce genotoxic effects which may cause heritable damage or lead to cancer in humans.

Twenty five years ago Miller & Miller introduced their electrophilic theory which led the way for the use of qualitative/quantitative structure-activity relationships ((Q)SARs) in the **prediction of genotoxicity and carcinogenicity**. In general, genotoxic chemicals have the unifying feature that they are either **electrophiles** or can be activated to electrophilic reactive intermediates (proelectrophiles).

The electrophilic theory of genotoxic carcinogenicity has led to two main **(Q)SAR approaches** for modelling genotoxic chemicals: a) to identify the electrophilic functional groups or substructures, i.e. to develop SAR models based on **structural alerts** (SAs); and b) to find **molecular descriptors** which can be quantitatively related to the activity of the chemicals, i.e. to develop QSARs. Most studies have provided qualitative models (SARs), which provide a "coarse-grain" approach for the identification of genotoxic potential. In addition, although more challenging, numerous studies have attempted to develop quantitative models (QSARs), which provide a more precise means of assessing genotoxicity and carcinogenicity, mainly for congeneric sets of chemicals.

To date, hundreds of (Q)SAR models have been published in the literature for predicting genotoxicity. The most commonly **modelled endpoint** for genotoxicity has been **Ames test mutagenicity**. It is concluded that the most useful models of regulatory point of view are those which are implemented in software tools and associated with transparent documentation on the model development and validation process.

An overview of the main **commercially and publicly available software tools** for predicting genotoxicity and carcinogenicity of chemicals, including industrial chemicals regulated under REACH, is given in the following table.

OSIRIS Results Highlights

Software	Availability	Comments (endpoints predicted, applicability and performance)
CAESAR http://www.caesar-project.eu/	Freely available	Mutagenicity, carcinogenicity
DfW (Lhasa Ltd.) http://www.lhasalimited.org	Commercial	Mutagenicity, chromosome damage, genotoxicity, carcinogenicity, peroxisome proliferation
GAP – Genetic Activity Profile Database developed by US EPA	Not readily available. Used in-house by US EPA	Data on 299 chemicals compiled by IARC and US EPA. Data are available on 299 compounds selected from volumes 1-50 of the IARC Monographs and on 115 compounds identified as Superfund Priority Substances.
HazardExpert http://www.compudrug.com	Commercial	Mutagenicity, oncogenicity
Lazar http://lazar.in-silico.de	Freely available	Ames mutagenicity, carcinogenicity
MDL-QSAR http://www.symyx.com/	Commercial	Carcinogenicity
MolCode Toolbox http://molcode.com/	Commercial	Ames mutagenicity, carcinogenicity
Multicase (MCASE/MC4PC) – MultiCASE Inc http://www.multicase.com	Commercial	Research tool - applies a statistical approach that automatically identifies molecular substructures that have a high probability of being relevant to the observed biological activity. Requires a learning set comprised of a mix of active and inactive molecules of diverse composition.
OASIS – TIMES http://oasis-lmc.org	Commercial	Ames mutagenicity, chromosomal aberrations
OECD Toolbox http://toolbox.oasis-lmc.org	Freely available	Includes two so-called "profilers" associated with genotoxicity and carcinogenicity, as well as three databases with experimental data that can be used to support grouping and read-across
OncoLogic™ http://www.epa.gov/oppt/sf/pubs/oncologic.htm	Freely available	Carcinogenicity
PASS – Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Moscow http://www.chem.ac.ru/Chemistry/Soft/PASS.en.html	Commercial	Classification models giving probability of mutagenic effects. There are two models, one for Ames mutagenicity, and another covering multiple *in vitro* and *in vivo* mutagenicity endpoints in mammals.
TOPKAT (Accelrys) http://www.accelrys.com	Commercial	Ames mutagenicity, carcinogenicity
Toxtree http://ecb.jrc.ec.europa.eu/qsar/	Freely available	Includes modules for mutagenicity, carcinogenicity, and the *in vivo* micronucleus assay

Reference

Miller E, Miller J 1981. Searches for ultimate chemical carcinogens and their reactions with cellular macromolecules. Cancer 47: 2327-2345

Additional information: Serafimova R, Fuart Gatnik M, Worth A 2010. Review of QSAR models and software tools for predicting genotoxicity and carcinogenicity 2010. JRC Scientific and Technical Reports. EUR 24427 EN - 2010. http://ecb.jrc.ec.europa.eu/DOCUMENTS/QSAR/EUR_24427_EN.pdf

OSIRIS Results Highlights

Comparative analysis of QSAR model pK_a prediction performances

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

Physiologically based pharmacokinetic (PBPK) modelling attempts to address the behaviour and fate of chemical compounds in human bodies by mathematical modelling. In order to produce sufficiently realistic results, PBPK models require reliable input data to characterise the chemical to be modelled. In the typical case of the absence of respective accurate experimental input data, estimation models need to be utilised. Thus, the performance of a PBPK model depends on the quality of the input of estimated data. One important topic addressed within OSIRIS in this context is the comparative analysis of **QSAR models for predicting the acid dissociation constant** pK_a of organic oxygen acids and nitrogen bases from molecular structure. pK_a is not only a crucial parameter for PBPK modelling but is also of high relevance in environmental fate modelling, ecotoxicity and toxicity in general.

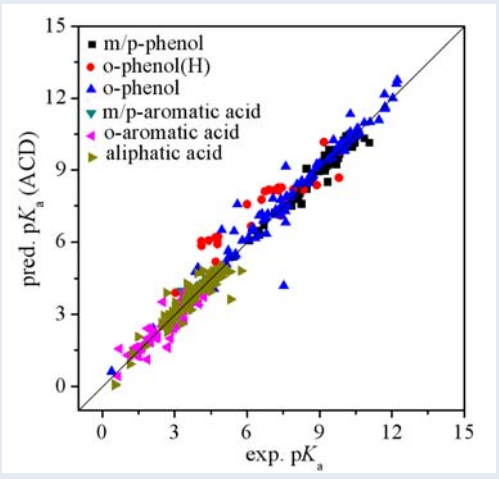
In aqueous solutions, **proton transfer between ionisable organic compounds and water** plays an important role for their speciations, which in turn affects their propensity of sorption to soil and sediment by cation exchange and determines their mobility, reaction kinetic, bioavailability, complexation, etc. The degree of dissociation of a Brönstedt acid AH governs both its **overall solubility** as well as the **pharmacokinetic properties** such as absorption, distribution, metabolism and excretion (ADME).

During the last years, different pK_a prediction methods from molecular structure have been developed, covering both **ionising groups of proteins** as well as **small organic acids and bases**. A prominent approach is developing models based on Hammett-type linear free-energy relationships (**LFERs**). A respective example is ACD, which is a commercial software package. SPARC employs a similar methodology, but uses functional groups rather than compound classes for defining reference pK_a values as starting point of the calculation. **Quantum chemical approaches** addressing both gas-phase and aqueous solvation have also been typically applied to smaller data sets.

A **comparative analysis of pK_a prediction performances** of ACD, SPARC and two calibrations of a semiempirical quantum chemical (QC) AM1 approach has been developed on 1143 organic compounds comprising 580 oxygen acids (phenols, aliphatic and aromatic carboxylic acids) and 563 nitrogen bases (anilines, aliphatic amines, N-heterocycles) that cover more than **17 orders of experimental pK_a** (from -5.00 to 12.23). The results show significant variations of methods in prediction quality across compound subsets as well as respective pitfalls related to specific structural patterns.

ACD appears to be superior to SPARC as well as to the semiempirical quantum chemical approach (QC and r-QC) based mainly on local donor delocalisability, with rms (root-mean-square error) values ranging from 0.12 to 1.21 pK_a units, and mean absolute errors from 0.07 to 0.97 pK_a units. The squared correlation coefficients r^2 are 0.86 to 0.96 (acids) and 0.79 to 0.95 (bases) for ACD, 0.77 to 0.95 (acids) and 0.85 to 0.97 (bases) for SPARC, and 0.64 to 0.87 (acids) and 0.43 to 0.83 (bases) for the QC methods, respectively.

Results also show that ACD, SPARC and QC models differ significantly with respect to their methodologies, which in turn affect their performance on the **structure type of interest**. This provides an opportunity for their application as parts of a consensus modelling approach.



Predicted vs. experimental pK_a for ACD applied to 580 organic oxygen acids, covering six subsets of phenols and carboxylic acids (o-phenol(H) represents ortho-substituted phenols with intramolecular H bonding).

Additional information: Yu H, Kühne R, Ebert R-U, Schüürmann G 2010. Comparative analysis of QSAR models for predicting pK_a of organic oxygen acids and nitrogen bases from molecular structure. J. Chem. Inf. Model., accepted

OSIRIS Results Highlights

Case studies for *in vitro* based Bioconcentration Factor prediction

University of Bern, Centre for Fish and Wildlife Health, Bern, Switzerland; Istituto di Ricerche Farmacologiche "Mario Negri", Laboratory of Environmental Chemistry and Toxicology, Milan, Italy

The **Bioconcentration Factor** (BCF) expresses the ratio of the steady state chemical concentration in aquatic water-respiring organisms and the chemical concentration in the water. In a regulatory context, it is usually the BCF determined in fish that is employed to identify bioaccumulative substances.

REACH requires testing of the bioconcentration potential in fish for chemicals with log $K_{ow} \geq 2.7$ that are produced at > 100 tons per year. The toxicological test procedure usually applied to determine bioconcentration in aquatic organisms is the *in vivo* fish test according to the OECD Test Guideline 305, which is associated with high animal use (n = 108 fish per test).

However, use of *in vivo* BCF data in chemical regulations suffers from a number of problems. First, ***in vivo* bioconcentration tests** are time-consuming, technically difficult and costly to perform, especially for high K_{ow} chemicals that possess the highest bioaccumulation potential. Secondly, the existing database on BCFs is rather limited.

Work in OSIRIS aimed to explore the principle suitability of **primary (freshly isolated) fish hepatocytes as *in vitro* system** to generate chemical biotransformation data that can be used to predict *in vivo* BCF. To this end, case studies were performed with benzo(a)pyrene as model substance, different *in vitro* assay conditions, and different physiological models to extrapolate from the *in vitro* metabolic rate values to the *in vivo* BCF values. Hepatocytes are the main site of xenobiotic metabolism in fish and previous studies have shown that isolated fish hepatocytes in principal maintain the capability of chemical biotransformation. The experiments were performed with rainbow trout as this is a **representative cold-water fish species** and, as such, is frequently used in bioaccumulation testing. As model substance, benzo(a)pyrene was used as a **prototypic metabolisable xenobiotic**. The metabolic clearance values determined in the hepatocytes ***in vitro* were scaled up to the fish *in vivo*** by adapting a physiologically-based extrapolation model originally developed for the use with *in vitro* microsome preparations, and were compared to a related model suggested by Han et al. (2007).

The results from this study show that isolated trout heaptocytes are principally suitable to determine metabolic clearance rates of xenobiotics. The *in vitro* determined metabolic clearance values can be upscaled by using **physiologically-based extrapolation models** to predict *in vivo* BCF values.

However, the study has also identified the current **limitations** in using *in vitro* hepatocyte assays as alternative to *in vivo* BCF testing: Metabolic clearance values as determined *in vitro* vary in relation to physiological parameters of the donor fish (e.g., seasonal status) and technical parameters of the *in vitro* assay (e.g., cell density). The latter source of variability can be eliminated by establishing a standardised protocol for the assay. A mean to overcome physiology-caused variability would be the use of cryopreserved hepatocytes. Investigations exploring the feasibility of this approach are currently ongoing. Moreover, predictions of *in vivo* BCF values from *in vitro* measured clearance values vary in relation to the prediction model used. The differences between the two models applied in this study come mainly from differences in parametrisation, i.e. use of different values for physiological parameters such as blood flow, liver size, hepatocellularity, etc. This is due to the fact that only few data on basic physiological parameters of fish are available. This highlights again that applied research can be only successful if there has been sufficient basic research.

Additional substances will be tested in order to clarify if the good *in vitro* – *in vivo* correlation found also applies to other substances and chemical groups.

Reference

Han X, Nabb D, Mingoia R, Yang C 2007. Determination of xenobiotic intrinsic clearance in freshly isolated hepatocytes from rainbow trout (Oncorhynchus mykiss) and rat and its application in bioaccumulation assessment. Environ. Sci. Technol. 41: 3269-3276

Third OSIRIS Training Course: Programme

The Third OSIRIS Training Course will be held on **3–5 November 2010** at the **Mario Negri Institute** in **Milan, Italy**.

The course addresses **risk assessment under the REACH** legislation with particular emphasis on non-testing methods and their use into a more global framework to set preferences in testing strategies and priorities.

A special section of the course is devoted to the **practical applications of QSAR** (qualitative or quantitative structure-activity relationships) and **expert systems tools** for predicting a human endpoint (i.e. genotoxicity) and an environmental endpoint (i.e. bioconcentration factor). A number of case studies will be presented and developed with the participants.

More information on the programme, venue and registration is available on the OSIRIS website **www.osiris-reach.eu**.

Programme

Day 1: Risk assessment, *in vitro* and *in silico* methods
3 November 14:00-17:45

- Introduction on risk assessment, risk analysis, risk management, and Integrated Testing Strategies (ITS) within the REACH regulatory framework
- Read-across: Approach and demo
- Exposure Based Waiving strategy for environmental endpoints
- Guidance on decision analytic modelling under REACH: The case of genotoxicity
- OSIRIS ITS Webtool
- OSIRIS Chemical Space Navigation Tool

Day 2: Integrated Testing Strategies for the environmental endpoint bioconcentration factor (BCF) and the human endpoint genotoxicity
4 November 9:15-17:30

- Bioaccumulation: *in silico* modules in the ITS framework
- ChemProp and its use for BCF
- Multiple tools for BCF predictions: Comparison, integration, applicability domain
- Role of *in vitro* methods to assess BCF
- OSIRIS ITS for BCF
- *In vitro* test methods (bacterial and mammalian) and *in silico* methods for industry in-house decision making: how the lessons learned in the regulatory assessment of industrial chemicals is applied
- Regulatory use of genotoxicity data
- Analysis of the relationships between *in vivo*, *in vitro*, and computational data for assessing mutagenicity and genotoxicity, their inherent uncertainties, and their possible integration in ITS
- The new DNA-binding profiler in the OECD (Q)SAR Application toolbox. Approach and demo
- The ITS scheme for genotoxicity

Day 3: Practical session with case studies
5 November 9:00-13:00

- Case study on BCF prediction/ITS: Demo and discussion
- Case study on genotoxicity prediction/ITS: Demo and discussion

Photos: Andrea Richarz

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

- Escher SE, Tluczkiewicz I, Batke M, Bitsch A, Melber C, Kroese DE, Buist HE, Mangelsdorf I 2010. Evaluation of inhalation TTC values with the database RepDose. Regul. Toxicol. Pharmacol. 58 (2): 259-274
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Conference Calendar: OSIRIS-related Events

Human Toxicology Project Symposium: Accelerating Implementation of the NRC Vision for Toxicity Testing in the 21st Century
9 – 10 November 2010, Washington, DC, USA
http://htpconsortium.wordpress.com/

12th Cefic-LRI Annual Workshop
17 – 18 November 2010, Brussels, Belgium
Reduction of Uncertainty Enabling Decision Making
http://www.cefic-lri.org/eventsmanager/37/30/12th-Cefic-LRI-Annual-Workshop

EPAA Annual Conference 2010
30 November 2010, Brussels, Belgium
European Partnership for Alternative Approaches to Animal Testing:
« Reduction and Refinement: Combining Excellence in Science and Animal Welfare »
http://ec.europa.eu/enterprise/epaa/3_2_conf_2010.htm

EMEC11 – 11th European Meeting on Environmental Chemistry
8 – 11 December 2010, Portoroz, Slovenia
http://sabotin.ung.si/~emec11/

6th Annual International Conference on Predictive Human Toxicity and ADME/Tox Studies
27 – 28 January 2011, Brussels, Belgium
http://www.mondialresearchgroup.com/index.php?whereTo=humt11

3rd SETAC Europe Special Science Symposium
2 – 3 February 2011, Brussels, Belgium
Prospective and retrospective environmental risk assessment of mixtures: moving from research to regulation
http://sesss03.setac.eu/

SOT 2011 – 50th Society of Toxicology Annual Meeting
6 – 10 March 2011, Washington, D.C., USA
http://www.toxicology.org/AI/MEET/AM2011

SETAC Europe 21st Annual Meeting
15 – 19 May 2011, Milan, Italy
http://milano.setac.eu/

Occupational and Environmental Exposures of Skin to Chemicals Conference (OEESC)
5 – 8 June 2011, Toronto, Canada
http://www.oeesc.org/

9th International Conference on Chemical Structures ICCS
5 – 9 June 2011, Noordwijkerhout, The Netherlands
http://www.int-conf-chem-structures.org/

15th International Symposium on Toxicity Assessment (ISTA 15)
3 – 8 July 2011, Hong Kong
hhttp://www.cityu.edu.hk/bch/ista15/

Environmental Health Risk 2011
25 – 27 July 2011, Riga, Latvia
6th International Conference on the Impact of Environmental Factors on Health
http://www.wessex.ac.uk/11-conferences/environmentalhealthrisk-2011.html

Reduced Animal Testing
28 – 29 July 2011, Zurich, Switzerland
http://www.mondialresearchgroup.com/index.php?whereTo=ratest

8th World Congress on Alternatives & Animal Use in the Life Sciences
21 – 25 August 2011, Montréal, Canada
http://www.wc8.ccac.ca/

EUROTOX 2011
28 – 31 August 2011, Paris, France
http://www.eurotox.com/pag.asp?ID_pagina=68

Preview of more 2011/2012 events:
www.osiris-reach.eu > Events and Activities

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