OSIRIS Newsletter

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Photo: Wolfgang Jarzen

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Fourth OSIRIS Annual Meeting

The Fourth OSIRIS Annual Meeting will take place **on Wednesday 30 March—Friday 1 April 2011 in Barcelona, Spain** at the University of Barcelona campus in the Barcelona Science Park.

The meeting will be hosted by the OSIRIS partner Universitat Rovira i Virgili (URV).

On the agenda:

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

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OSIRIS ITS Meeting

Delegates from several OSIRIS partner institutions met 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 for the human health and environmental endpoints

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

The status of all ITS was presented and remaining questions and further steps to be taken were discussed.

An overview of the ITS for the different endpoints is given on the following pages.

The ITS will be demonstrated to Stakeholders at the upcoming OSIRIS ITS Workshop (see p. 15).

Photos: Wolfgang Janzen

The OSIRIS Integrated Testing Strategies

Integrated Testing Strategies 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**, to group information about **similar substances** and to integrate **exposure considerations**. The different and possibly contradictory information is weighed and the respective uncertainties taken into account in a **Weight of Evidence (WoE) approach**.

Thus an ITS combines all available testing and non-testing data and concludes whether or not additional data is needed. In case of data gaps, the ITS proposes the most appropriate method to acquire the missing information. Ideally, with regard to the **3R principle** of replacement, reduction and refinement of animal testing, non-testing methods such as *in vitro* assays and QSAR (qualitative or quantitative structure-activity relationships) methods are preferred for this purpose. In addition, an optimisation framework has been developed, applying a Value-of-Information (VOI) approach to sequential testing strategies. This allows to conclude on the optimal test proposal given that information gains from testing have to be balanced against testing costs and animal welfare loss. The ITS use **endpoint-specific** testing and non-testing methods and weight their contribution (see also scheme on page 3):

- Step 1: Gather all substance-specific information (testing and non-testing data)
- Step 2: Add weight to type of information using statistical methods and/or expert knowledge
- Step 3: Conclude whether gathered information and/or performed *in vitro* testing are sufficient for classification & labelling (C&L) / risk assessment

If data are not sufficient for C&L or risk assessment – data gap is identified:

- Step 4: Gather information on structurally related chemicals to do read-across or category approach/ perform *in vitro* testing if technically possible and relevant for respective endpoint
- Step 5: Is Exposure-Based Waiving (EBW) an option? Are Thresholds of Toxicological Concern (TTC) an option? Does the compound belong to the applicability domain of TTC?
- Step 6: Propose animal testing as last resort.

Some specific issues of the ITS for the different endpoints are discussed in the following.

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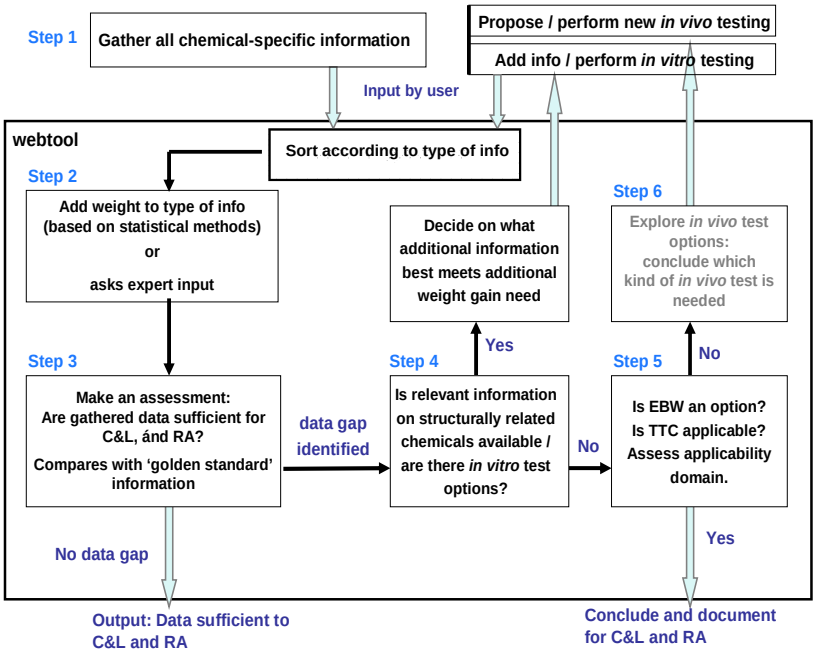

General scheme of the OSIRIS Integrated Testing Strategies for human health endpoints.

ITS Repeated Dose Toxicity

Repeated dose toxicity is a complex endpoint for which mode and mechanism of action are highly substance-dependent and normally not known. Unspecific cytotoxicity, receptor-induced toxicity or a combination of both may play a role. Moreover, complex biological processes as distribution, metabolism and elimination influence the overall toxicity. So far single or combined *in vitro* assays are not able to mimic all relevant *in vivo* processes and are thus not able to substitute parts or whole *in vivo* repeated dose studies. Therefore *in vitro* assays have neither been considered in step 2 nor step 6 of the repeated dose toxicity ITS.

Furthermore, only few QSAR methods for repeated dose toxicity have been described so far.

The ITS focuses on step 2, where the reliability/ relevance of the available testing data is assessed. In many cases, toxicity data of existing chemicals are available from "old" studies conducted before the publication of OECD guidelines. The results of these non-guideline studies are now considered as not reliable or only with restrictions. However, also "old" studies may be valid. This validity of the non-guideline study depends on the scope of examination and the overall quality of the study. Therefore a major focus of the repeated dose toxicity ITS – before concluding on the data gap and continuing with the following steps – is to assess data validity and specifically to which extent and under which conditions non-guideline studies are valid to be included in the risk assessment.

ITS Skin Sensitisation

In experimental testing often a minimum concentration causing sensitisation above a specific threshold can be observed. This concentration determines the skin sensitisation potential of a substance. For REACH, information on the skin sensitisation potential is not required, only information whether a substance in any concentration is capable of causing at least a 3 fold increase of the stimulation index in a Local Lymph Node Assay (LLNA). Therefore skin sensitisation is treated as a categorical (yes/no) endpoint in the OSIRIS ITS.

For this endpoint, a multitude of alternative methods is available: older test types, *in vitro* assays and a number of QSAR models predicting the ability to cause skin sensitisation. Bayesian decision theory is applied to calculate the probability for each single alternative and/or combination of these alternative methods that a test/model outcome is correct. All methods integrated in the ITS have to be characterised quantitatively in terms of sensitivity and specificity of predicting the required test result, i.e. the LLNA test. This probability (as a percentage) can subsequently be compared to the probability that the LLNA test is giving the "true" result after only one test. Thus an objective, transparent, but also strictly

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statistical threshold is generated which determines whether the available tests/models deliver sufficient "Weight of Evidence" to fulfil REACH registration purposes. The quantification of the "weight" of each method also creates the possibility to define the most optimal "next step" in testing.

The ITS considers available OSIRIS and public data:

- human: Patch Test data (HPT)
- *in vivo*: Guinea Pig Maximiation Test (GPMT) incl. Buehler assay, Murine Local Lymph Node Assay
- *in vitro*: Human Cell line activation test
- *in silico*: (QSAR) models, OASIS TIMES-S (Tissue Metabolism Simulator-Skin sensitisation), MultiCASE model (Danish EPA QSAR database), Derek for Windows (Lhasa ltd), SMARTs rules (LJMU), Accelrys TOPKAT.

Any other test or model predicting the endpoint skin sensitisation, which can be characterised in terms of its sensitivity and specificity in predicting the LLNA test, can be further included in this ITS.

ITS Mutagenicity & Carcinogenicity

The outcome of mutagenicity testing influences the subsequent concern and testing strategy for carcinogenic properties. Positive results in mutagenicity assays raise concern for (genotoxic) carcinogenicity and generally lead to precautionary labelling, whereas non-genotoxic carcinogens cannot be identified using mutagenicity testing. Genotoxic carcinogens can further be subdivided in substances that directly react with DNA molecules, and substances that induce genotoxicity indirectly. For a comprehensive coverage of the potential mutagenic properties of a substance, information on its ability to induce gene mutations, structural and numerical chromosomal aberrations is required.

The testing strategy of the ITS for **mutagenicity** according to the REACH requirements consists of a number of well accepted *in vitro* tests, each testing a different aspect of mutagenicity. They should be regarded as separate golden standards. *In vivo* tests have the function to select true *in vitro* positives, i.e. (existent) *in vivo* tests data overrule *in vitro* test results and can therefore also substitute the corresponding *in vitro* test. Consequently, the strategy changes when information is available, the next step depending not only on which information is available, but also on the conclusions drawn from it and the tonnage level.

The quantitative WoE approach weighs each available alternative *in vitro* test or tool for its ability to predict the outcome of the specific golden standard assay (e.g. gene mutations in bacteria).

Carcinogenicity studies have a qualitative categorical aspect comparable to mutagenicity studies, i.e. they should answer the question whether or not a substance is to be considered carcinogenic, as well as a quantitative continuous aspect comparable to repeated dose studies, i.e. in case the substance is carcinogenic, how potent it is. Studies that are adequate to answer the classification question may not be adequate to answer the potency question, while the reverse is well the case. Since the aim of the ITS for carcinogenicity is to establish whether the available information is sufficient to satisfy the REACH data requirements, the WoE approach is limited to the continuous aspect, as the categorical aspect will be implicitly included.

ITS Bioconcentration Factor

REACH identifies high bioaccumulation potential from the chemicals' bioconcentration factors (BCF) > 2000 (log BCF > 3.3, B chemicals) or > 5000 (log BCF > 3.7, vB chemicals). The ITS workflow is based on the REACH annexes VII-X, the ECHA guidance on information requirements and chemical safety assessment Chapter R.7c: endpoint specific guidance and Chapter R.11: PBT assessment. All necessary data requirements for the different regulatory purposes C&L, chemical safety assessment (CSA) and assessment of persistence, bioaccumulation and toxicity (PBT) have been taken into account. The suggested scheme explores the REACH regulatory requirements in order to identify test priorities and use of different methodologies such as QSARs, chemical categories, read–across, *in vitro* and *in vivo* testing methods for bioconcentration assessment.

Cut-off criteria for substance-specific waiving of experimental BCF studies have been included (see also p. 10). A large dataset of experimental BCF was used to test the rules of the waiving scheme: about 60% of the nB compounds were correctly identified as nB without false negatives. The same dataset was also used to verify the ability of the QSAR models to predict BCF. The present tools support to reduce testing for bioaccumulation by ~50% as compared to conventional assessment schemes.

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ITS Aquatic Toxicity

Aquatic toxicity refers to the intrinsic property of a substance to be detrimental to a water organism after short-term and/or long-term exposure. Aquatic risk assessment deals with three major compartments: pelagic, sediment and sewage toxicity. Aquatic pelagic toxicity refers to freshwater and marine organisms living in the water column. In general, it is assumed that aquatic toxicity is mainly related to the water-borne exposure of a substance and expressed as external concentration of that substance in test water.

The ITS workflow is limited to pelagic toxicity and it is based on the REACH annexes VII-X and the applicable ECHA guidance documents. All necessary data requirements for the different regulatory purposes (C&L, CSA and PBT assessment) have been taken into account. The ITS scheme identifies test priorities and explores the use of QSARs, read–across, *in vitro* and *in vivo* testing methods to assess aquatic toxicity.

Screening criteria for the time of degradation and an evaluation of the mode of action of the substances have been included. Tools to obtain information for aquatic toxicity required for the registration of a substance – mainly freely available software or tools developed within OSIRIS – have been added in the ITS scheme.

Weight of Evidence Approach

The frameworks developed integrate heterogeneous information gathered by several methods, including QSARs, TTC, read-across, *in vitro* and *in vivo* tests. These methods are affected by different sources of uncertainty which have to be identified, managed and reduced in subsequent testing cycles by using decision theory tools.

The quantification of uncertainties involves the consideration of probabilities. Bayesian statistics allow the weighting of prior information (including expert information) and information from testing. Moreover, the successive updating of the prediction probability is possible, if new, additional information is introduced. Thus, in a WoE, the result of sequentially adding existing information, or generating new information will show whether the confidence in the conclusion has increased. The order in which information from different sources is combined does not influence the calculated posterior probability.

In order to determine how much a single piece of information should contribute to the overall conclusion on the toxicological properties of a substance, the reliability and relevance of that information need to be assessed. This includes a judgement on the reliability and relevance of the individual data and the (scientific) validity of the methods used to generate these data. The different types of endpoints – categorical and continuous – require a different WoE approach. An overall weight factor represents the probability that the collected information will lead to a correct conclusion with respect to the goal it was collected for: classification in case of the categorical endpoints, a reliable potency estimate for the continuous endpoints.

As some of the weight factors have a statistical basis, and others depend to a large extent on expert judgement, a decision framework is needed in which both types of data can be combined. For human toxicological endpoints, dealt within this project, a Bayesian framework was chosen, while for environmental endpoints the Dempster-Shafer theory was preferred.

The Dempster-Shafer theory of evidence is a technique for decision-making under uncertainty which considers sets of hypotheses and assigns probabilities to them. It incorporates complex, even conflicting, information into a mathematical framework. Bayesian analysis is a special case within the Dempster-Shafer theory.

Value-of-Information Approach

A decision-analytic model for the prioritisation of chemicals for testing and the optimisation of sequential testing strategies has been developed. The model adopts a VOI approach describing the expected welfare gains (net of costs) from collecting additional information. The VOI model can be applied to both human health and environmental endpoints.

The VOI is the expected net benefit when using the substance if optimally regulated with additional information from testing, instead of using the substance regulated under uncertainty. Applying the VOI model to sequential testing strategies such as ITS allows for analysing how test selection is driven by the trade-off between the tests' diagnostic performance and testing costs. Furthermore, VOI analysis identifies the test that should be conducted first, the optimal sequence of tests, and it provides a stopping

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rule for testing. A test should be performed if and only if its VOI exceeds testing costs. In addition, the optimisation of sequential testing – which is considered a prerequisite for efficient risk management of testing – requires to weigh information gains against testing costs and to link them with the payoffs from taking action at any decision node of the sequence.

The OSIRIS Webtool

The methods and ITS developed within OSIRIS for the different human health and environmental endpoints are implemented in the webbased OSIRIS Tool, which will be made publicly available to end-users at the end of the project.

The functionalities of the OSIRIS Webtool include:

- substance entry
- data entry, with access to integrated databases
- assessment of information according to endpoints and REACH requirements
- expert judgement entry
- decision theory approaches, OSIRIS Consensus Tool
- Chemical Space Navigation Tool as visual aid for pre-screening tasks.

As a 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.

More information is available in the following related OSIRIS publications:

Aldenberg T, Jaworska JS 2010. Multiple test in silico Weight-of-Evidence for toxicological endpoints. In: Cronin MTD, Madden JC (eds): In Silico Toxicology: Principles and Applications, Royal Society of Chemistry, Cambridge, UK, pp. 558-583

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. 57 (2-3): 157-167

Fernández A, Rallo R, Giralt F 2009. Uncertainty reduction in environmental data with conflicting information. Environ. Sci. Technol. 43 (13): 5001-5006

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. Reg. Toxicol. Pharmacol. 58 (3): 408-420

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

Nendza M, Müller M 2010. Screening for low aquatic bioaccumulation (1): Lipinski's 'Rule of 5' and molecular size. SAR and QSAR in Environmental Research 21 (5&6): 495-512

Gabbert S, Van Ierland EC 2010. Cost-effectiveness analysis of chemical testing for decision-support: How to include animal welfare? Hum. Ecol. Risk. Assess.16 (3): 603-620

For a complete OSIRIS publication list see www.osiris-reach.eu > Publications.

Third OSIRIS Training Course

The OSIRIS Training Courses specifically target professional end-users in industry and regulatory agencies involved in the submission and review of chemical risk assessments. They aim is to introduce the main concepts underlying the design of Integrated Testing Strategies (ITS), giving particular emphasis on non-testing methods such as QSARs (qualitative or quantitative structure-activity relationships), chemical grouping and read-across.

The Third OSIRIS Training Course has been held on **3–5 November 2010** at the **Mario Negri Institute** in **Milan, Italy**. The course addressed the conceptual background of risk assessment and ITS as well as methods developed within OSIRIS.

Risk assessment, *in vitro* and *in silico* methods

The first day started with an introduction on risk assessment, risk analysis, risk management and ITS within the REACH regulatory framework. The approaches of read-across and exposure-based waiving, components of the ITS, were explained and decision analytic modelling under REACH was introduced for the case of genotoxicity. The concept and functions of the OSIRIS ITS Webtool and the integrated Chemical Space Navigation Tool were presented. The OSIRIS Webtool implements the ITS components developed within the project and will be made available to the public.

Integrated Testing Strategies for the endpoints bioconcentration factor (BCF) and genotoxicity

On the second day, different aspects of ITS for the environmental endpoint BCF and the human health endpoint genotoxicity were addressed. An overview was given of different types of alternative (chemistry-driven and *in silico*) modules for environmental bioaccumulation assessment in the ITS framework. Different tools for BCF prediction were compared – including the software ChemProp –, emphasising uncertainty and applicability domain issues. The use of *in vitro* methods in bioaccumulation assessment was analysed. Moreover, the OSIRIS ITS on BCF implemented in the Webtool was demonstrated. Regarding the endpoint genotoxicity, an overview was given of the use of bacterial and mammalian *in vitro* test methods and *in silico* methods for industry in house decision making as well as of the regulatory use of genotoxicity data. Available *in vitro* and *in silico* tools to assess mutagenicity and cancerogenicity and new future perspectives were analysed. The new DNA-binding profiler in the OECD QSAR Application toolbox was demonstrated and the ITS scheme for genotoxicity developed within OSIRIS was presented.

Practical session with case studies

The third day was devoted to the practical application of QSAR and expert systems tools. Hands-on experience was provided to the course participants for different *in silico* tools to predict the BCF. The results were compared and aspects of uncertainty were discussed. After an introduction on the principles of QSAR and available software tools, a workflow for the assessment of the genotoxic potential of chemicals by means of *in silico* methods was presented. A case study provided hands-on experience on using different genotoxicity *in silico* prediction tools.

Photos: Wolfgang Janzen, Andrea Richarz

Last but not least the course participants enjoyed Italian hospitality in a Sardinian restaurant with fish in every possible variation as well as a Milanese aperitivo.

OSIRIS Results Highlights

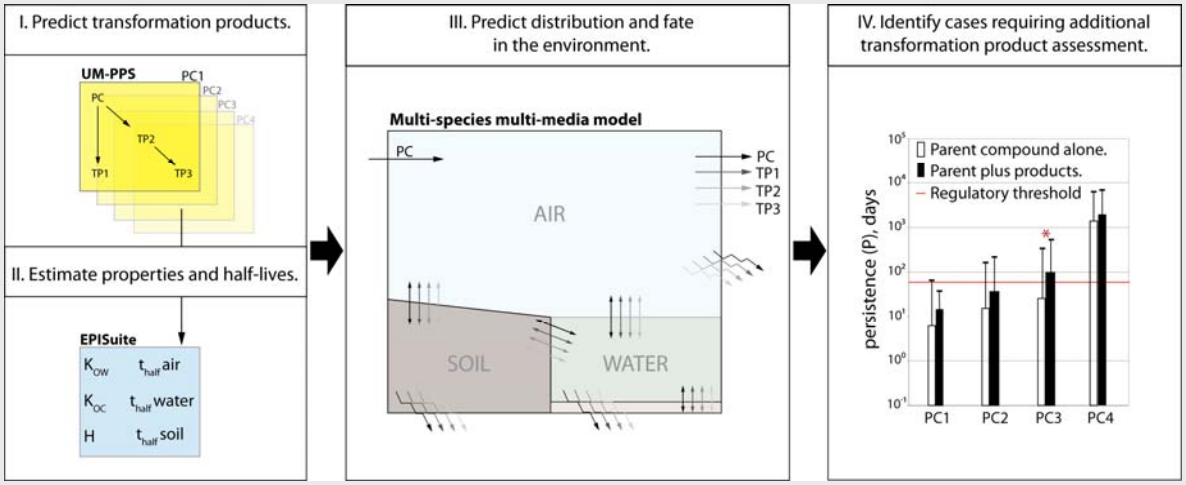
A screening method for transformation product persistence (Partner ETHZ)

ETH Zurich, Safety and Environmental Technology Group, Zurich, Switzerland

REACH requires that 'significant' **transformation products** be included in **assessments for chemicals** produced or imported at more than 100 tonnes per year. The implementation of this requirement will be extremely challenging, due to the **lack of available data** and reliable quantitative-structure activity relationships (QSARs) for the ill-defined chemical space of degradation products. As part of the OSIRIS project's evaluation of environmental exposure assessment under REACH (Pillar 3), ETH Zurich has been working on **models** that simultaneously treat the **fate of parent** (emitted) **chemicals** and their **transformation products** in the environment. However, application of such models presupposes the availability of property and degradation data for parent chemicals (PCs) and transformation products (TPs). The costs associated with the assessment of PCs alone (in terms of both money and test organisms) are already high, and the inclusion of an unspecified number of possibly important TPs could increase them exponentially. Thus, a procedure to **screen for potentially important TPs prior to testing** is highly desirable.

We have constructed a preliminary scheme to assess whether effective transformation product screening can be performed given current data limitations. It consists of four main elements: (i) prediction of TPs for a given PC; (ii) estimation of physico-chemical properties and degradation rates for the PC and its TPs; (iii) prediction of mass distributions in the environment, from which persistence can be calculated; (iv) comparison of predicted persistence, with and without the inclusion of TPs, to relevant thresholds (e.g. 60 day half-life).

The goal of the screening scheme is to **identify** for which chemicals the inclusion of TPs in persistence estimates would **change the classification of the PC** from non-persistent to persistent. To evaluate our screening scheme, we chose **22 test cases** for which biodegradation pathways are known and compared their classification with and without TPs to persistence classifications based on predicted products with estimated properties and half-lives. We included **uncertainties** around property and half-life estimates. Our scheme was able to identify the 8 cases out of 22 for which inclusion of TPs in persistence calculations could affect classification relative to a typical threshold half-life of 60 days. However, classification itself would not be possible using this scheme due to very high uncertainty with respect to media-specific half-lives and, to a lesser extent, physico-chemical properties like the Henry's Law coefficient. Our scheme provides a starting point for the **prioritisation of further experimental work** that is sorely needed to expand our knowledge about and confidence in degradation and partitioning properties for industrial chemicals and their transformation products.



Screening scheme to identify potentially important transformation products.

Additional information: Ng CA, Scheringer M, Fenner K, Hungerbühler K 2011. A Framework for evaluating the contribution of transformation products to chemical persistence in the environment. ***Environmental Policy: Past, Present and Future* Special Issue**. Env. Sci. Technol. 45 (1): 111–117, DOI: 0.1021/es1010237

OSIRIS Results Highlights

Non-animal bioassay excess toxicity for deriving structural alerts (Partner UFZ)

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

Electrophilic compounds are known to exert **reactive toxicity**, resulting in both severe human toxicology effects such as sensitisation and mutagenicity as well as in excess toxicity towards aquatic species. The primary molecular event of toxicological relevance is a covalent attack of the compound at nucleophilic sites of proteins or DNA, resulting in a chemical modification of the biomolecule.

Targeted **non-animal bioassays** can sense certain types of **potentially electrophilic structures** for their actual potential to exert excess toxicity due to electrophilic reaction mechanisms. A respective set of **structural alerts** would allow one to identify – at an early stage of chemical safety assessment – those compounds that require more detailed investigation because of their electrophilicity-driven potential for reactive toxicity.

The marine bacterium *Vibrio fischeri* is able to yield bioluminescence and has been widely used as test organism for screening the aquatic toxicity of chemicals. In this investigation *Vibrio fischeri* have been employed to extend and refine structural alerts as non-test instrument for predicting reactive toxicity.

Epoxides, i.e. electrophilic three-membered cyclic ethers with a substantial ring strain, which can undergo ring-opening through a reaction with nucleophiles (NuH, Figure 1), were investigated.

A **short-term toxicity test** (quantifying the compound concentration yielding 50% inhibition of *Vibrio fischeri* bioluminescence after 30 min exposure) was combined with a **long-term growth inhibition assay** (24h exposure) to determine the reactivity of electrophile compounds in comparison to narcosis-level compounds.

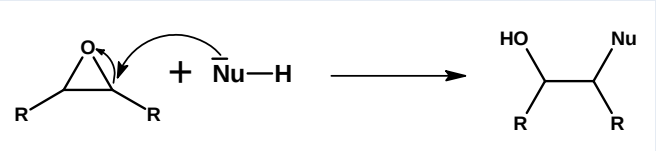


Figure 1: SN_2-type ring-opening of epoxides through a reaction with a nucleophile NuH.

For both test systems **baseline narcosis models** were derived through analyses of 19 organic narcotics. In addition, the toxicities of 15 aliphatic and nonaliphatic epoxides were measured (Figure 2). **Toxicity enhancement** (Te) as the ratio of narcosis-predicted over experimental EC_{50} values was afterwards determined to find compounds with hazard potential and to derive structural alerts.

The seven aliphatic epoxides did not show enhanced toxicity compared to narcotic substances in the short-term test as well as in the long-term test. However, the eight nonaliphatic epoxides were excess toxic. Thus, only substructures as e.g. ether or phenyl groups in addition to epoxide groups yielded enhanced toxicity due to electron withdrawing activation of the epoxide group.

Furthermore, the acute toxicity test was found to be slightly more sensitive than the chronic toxicity test, a result to be further explored.

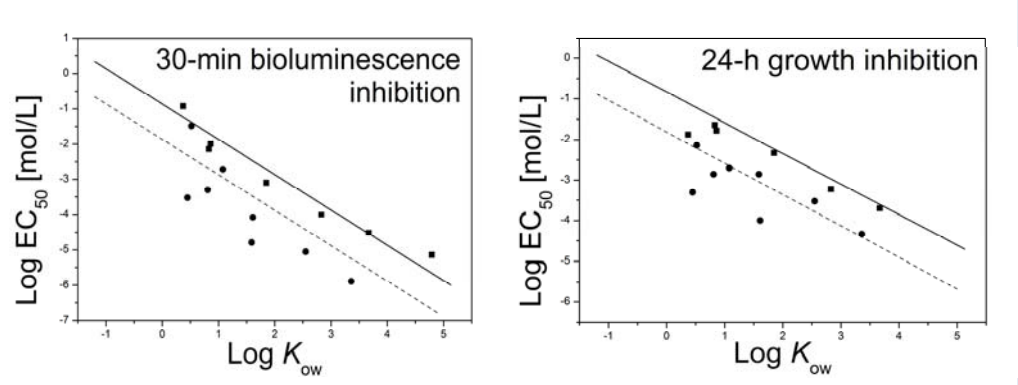


Figure 2: Left short-term (30-min) bioluminescence inhibition and right long-term (24-h) growth inhibition of aliphatic (■) and non-aliphatic (●) epoxides towards the bacteria *Vibrio fischeri*. The solid line represents baseline narcosis, and the broken line the threshold log *Te* = 1 (toxicity enhancement) for discriminating between narcosis-level and excess toxicity.

Additional information: Blaschke U, Paschke A, Rensch I, Schüürmann G 2010. Acute and chronic toxicity toward the bacteria *Vibrio fischeri* of organic narcotics and epoxides – Structural alerts for epoxide excess toxicity. Chem. Res. Toxicol. 23 (12): 1936–1946, DOI: 10.1021/tx100298w

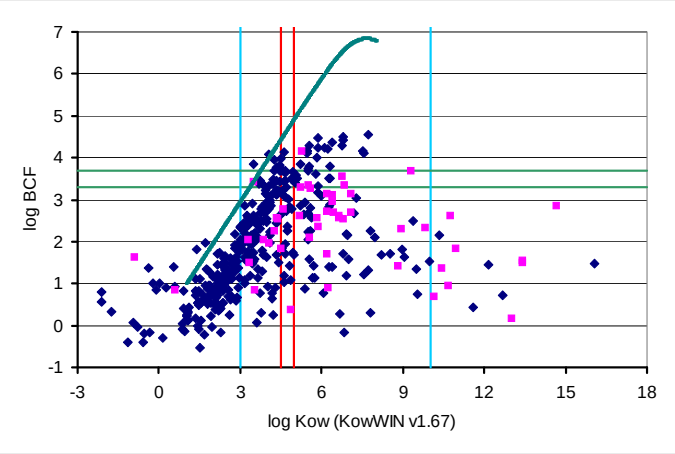
OSIRIS Results Highlights

Refined cut-off criteria for substance-specific waiving of bioassays (Partner AL)

Analytisches Laboratorium, Luhnstedt, Germany

According to REACH, substances of very high concern, such as (very) persistent, (very) bioaccumulative and toxic (**PBT, vPvB**) chemicals require authorisation, and their use may be restricted. REACH identifies high bioaccumulation potential from the chemicals' bioconcentration factors (BCF) > 2000 (log BCF > 3.3, B chemicals) or > 5000 (log BCF > 3.7, vB chemicals).

The aim of the present work is to protectively **de-prioritise nonB compounds** with BCF < 2000. Major emphasis is put on 'safe' criteria, **excluding false negatives**, though at the cost of considerable fractions of false positives. Eventually, experimental BCF studies for chemicals with bioavailability constraints may be waived because they either provide **no risk-relevant information** or are **unworkable to perform**. So far, bioconcentration cut-off criteria have been focussed on molecular size, assuming that membrane permeation of large molecules is limited. However, no robust evidence was found for cut-offs in bioconcentration related to **molecular size**. Rather, a modulating effect of molecular size on membrane permeation appears to exist. Moreover, the ensemble of molecular attributes according to **Lipinski's 'Rule of 5'**, molecular weight (MW), hydrogen bonding capacity and lipophilicity expressed as 1-octanol/water partition coefficient (log K_{OW}), was found to be inadequate to identify nonB compounds. Possible reasons are key differences in the dominating processes during oral absorption of pharmaceutical drugs (bulk dissolution) and the uptake of waterborne environmental contaminants by aquatic organisms (continuous low-level exposure). However, **pragmatic thresholds** in two individual attributes, MW (> 650 g/mol) and log K_{OW} (< 3 or > 10, see Figure), have been verified on three independent datasets (existing industrial chemicals, pesticides and new chemicals, known B/vB compounds) to **safely de-prioritise 30 to 40 % of chemicals of low concern** with regard to the B criterion.[1]



Empirical relationship between log K_{OW} and log BCF. The bilinear function describes the maximum accumulation potential (Nendza 1991). The horizontal green lines indicate B (BCF < 2000) and vB (BCF < 5000) criteria. The vertical lines indicate cut-off criteria in log K_{OW} at 3 or 10 (blue lines, TGD (ECB 2003)), at 4.5 (red line, ECHA (2008) screening criterion for PBT assessment) and at 5 (red line, Lipinski et al. 1997). ♦: data from CEFIC LRI compilation on bioconcentration (EURAS 2007), ■: data from pesticides and new chemicals' registration (German Environment Agency).

Further search for protective screening criteria to indicate nonB chemicals supports *in silico* PBT assessments based on **physico-chemical properties** related to mediaspecific exposures and bioavailability. The primary logic is that only if a compound is present in the water in any form (determinants: water solubility, degradability, vapour pressure), it may be taken up by organisms (determinants: log K_{OW}, p*Ka*). The classification scheme has been improved by combination of physico-chemical parameters (**lipophilicity, ionisation, Henry's law constant** (presumably combining information about water solubility and volatility) and stability in water phases (in terms of **hydrolysis** and ready **biodegradability**)) in a binary decision tree to **reliably identify ~50% nonB compounds (BCF < 2000)**. If polybrominated compounds (> 4 Br), organometallics, compounds with perfluorinated fragments, substances with an acyclic alkyl moiety (chain length > C7) or thiols are excluded from the applicability domain, no false negatives have been detected (**sensitivity of 100 %**).[2]

References

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OSIRIS Results Highlights

ECB (European Chemicals Bureau) 2003. Technical guidance document on risk assessment in support of Commission Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No 1488/94 on risk assessment for existing substances, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Doc. EUR 20418 EN/1, European Communities

ECHA 2008. Guidance on information requirements and chemical safety assessment, Chapter R.11: PBT assessment

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 23: 3-25

EURAS 2007. CEFIC LRI Goldstandard Database, http://ambit.acad.bg/ambit/php/euras.php

More information is available in the full articles:

[1] Nendza M, Müller M 2010. Screening for low aquatic bioaccumulation (1): Lipinski's 'Rule of 5' and molecular size. SAR and QSAR in Environmental Research 21 (5&6): 495-512 , DOI: 10.1080/1062936X.2010.502295

[2] Nendza M, Herbst T 2011. Screening for low aquatic bioaccumulation (2): Physico-chemical constraints. SAR and QSAR in Environmental Research 22 (1&2): in press

Derivation of threshold values for inhalation exposure (Partners FhG, TNO)

Fraunhofer Institute of Toxicology and Experimental Medicine, Hanover, Germany
TNO Quality of Life, Zeist, The Netherlands

The **Threshold of Toxicological Concern** (TTC) concept is one constituent of the integrated testing strategy for chronic toxicity developed within OSIRIS. If human exposure does not exceed the defined TTC limit values, no risk to human health is expected. TTC values are used for the risk assessment of substances when there are no toxicological data available or testing is not possible for technical reasons. TTC have already been used successfully to regulate e.g. food contaminants and flavourings substances.

Based on the substances' structural properties, the TTC concept distinguishes three substance classes and their corresponding thresholds by means of the **Cramer decision tree**. Cramer classes 1 and 2 include substances whose structure suggests low/moderate toxicity, while Cramer class 3 contains all substances with predominantly reactive structural groups which are expected to cause toxic effects. The Cramer decision tree is based on theoretical considerations and was already developed in 1978 to assess systemic toxicity. In 1996, Munro made use of the Cramer classes to derive TTC values for **oral exposure**. To this end, he developed a database commonly referred to as **Munro database**, which contains the NOEL and LOEL values (No Observed Effect Level and Lowest Observed Effect Level) of over 600 substances from mostly sub-chronic and chronic studies in rats, mice, hamsters, and rabbits. The threshold values he derived were 1800 µg/person/day for Cramer class 1, 540 µg/person/day for Cramer class 2, and 90 µg/person/day for Cramer class 3.

Inhalation is an important route of **exposure** to chemicals at the workplace. In this investigation it has been evaluated whether and to what extent the TTC concept is suitable for deriving threshold values for substances taken up by inhalation. TTC values for inhalation exposure to non-genotoxic substances were derived by using the FhG database RepDose (www.Fraunhofer-RepDose.de).

In the **RepDose database**, 203 industrial chemicals were identified that have already been tested in repeated-dose inhalation studies. Threshold values were derived by using an analogous method to that developed by Munro, and these were 4 µg/person/day for Cramer class 1 and 71 µg/person/day for Cramer class 3. No value could be derived for

	Number of compounds	TTC (µg/person/day) for Cramer class #	
		1	3
All compounds	203	71	4
Non-genotoxic	136	180	4

Inhalation TTCs derived for consumers based on the RepDose database.

exposure: 24h/day and 7days/week

OSIRIS Results Highlights

Cramer class 2, as this class included only a very small number of substances (4%).

The derived thresholds for inhalation exposure are **significantly lower than** the TTC values for **oral exposure**. It has been demonstrated that one reason for the observed difference between inhalation and oral thresholds is the **sensitivity of the respiratory tract to local effects.** Local effects in the respiratory tract are frequently observed, even at low exposure concentrations, and thus determine the NOEC.

In a next step, all substances with structural alerts for genotoxicity were excluded, since genotoxic substances are regulated by a specific TTC value of 0.15 µg/person/day. This resulted in the following TTC values for non-genotoxic substances: 180 µg/person/day for Cramer class 1 and 4 µg/person/day for Cramer class 3.

Under the European Regulation REACH, risk assessments of thousands of chemicals will be required within the next few years. Together with the oral TTC values already described in the literature, the inhalation thresholds derived in this work represent a useful and transparent method allowing to avoid animal testing if the exposure is below the substance-specific threshold value. By taking into account route-specific differences, it will be possible to further improve the TTC concept and thus also the corresponding thresholds.

Additional information: Escher SE, Tluczkiewicz I, Batke M, Bitsch A, Melber C, Kroese ED, Buist HE, Mangelsdorf I 2010. Evaluation of inhalation TTC values with the database RepDose. Reg. Toxicol. and Pharmacol. 58: 259-274, DOI: 10.1016/j.yrtph.2010.06.009

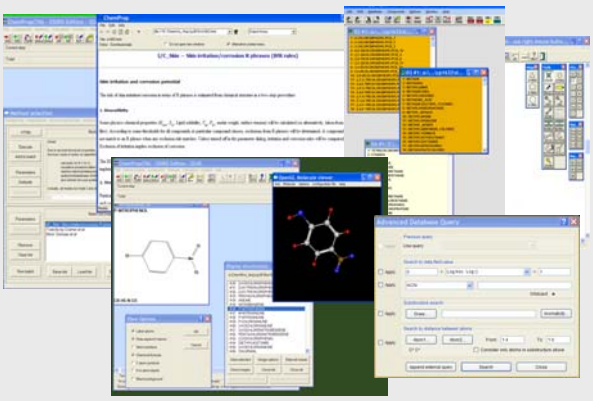
ChemProp, an *in silico* tool for prediction of chemicals' properties and toxicity

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

Developed by OSIRIS partner UFZ, the software system ChemProp predicts compound properties from chemical structures by means of **qualitative/quantitative structure-activity relationships** (QSARs) and contains **databases** with compound properties.

The database module supports structure searching in external SQL resources (typically Excel files) and in WWW resources (via eMolecules). **Substructure searching** facilities are implemented for internal and external resources, together with a graphical substructure query editor. The database currently contains ca. 15,000 entries including conformers and specific tautomers, covering more than 10,000 different chemicals. **OSIRIS datasets** of (eco-) toxicological test results are accessible as external databases via ChemProp.

ChemProp includes **QSAR methods** for physicochemical, ecotoxicological and toxicological endpoints. The OSIRIS edition of the ChemProp software is currently offering ca. 80 models for predicting about 40 different properties regarding **partitioning, degradation, environmental fate, ecotoxicology** and **toxicology**. **Read-across models** based on atom-centred fragments (ACF) and **characterisation of the applicability domain**



with particular respect to the **chemical domain** by means of ACF are included.

Compounds can be imported via SMILES, existing files, e.g. in .SDF or .XML format, a graphical editor or by searching the ChemProp databases. The results of the detailed compound profiling are automatically summarised in a report for later documentation.

Following a presentation of OSIRIS in the European Chemicals Agency (ECHA), the OSIRIS edition of the ChemProp software was provided to ECHA and a respective training course took place in Helsinki in June 2010.

Release notes for the recent versions are available at http://www.ufz.de/index.php?en=7160.

New OSIRIS Publications

The complete publication list with **links to the articles** is available at **www.osiris-reach.eu** > Publications

Publications in Peer Reviewed Scientific Journals

- Fjodorova N, Vračko M, Tušar M, Jezierska A, Novič M, Kühne R, Schüürmann G 2010. Quantitative and qualitative models for carcinogenicity prediction for non-congeneric chemicals using CP ANN method for regulatory uses. Mol. Divers. 14: 581-594
- 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. Reg. Toxicol. Pharmacol. 58 (3): 408-420
- Heinlaan M, Kahru A, Kasemets K, Arbeille B, Prensier G, Dubourguier H-C 2011. Changes in the Daphnia magna midgut upon ingestion of copper oxide nanoparticles: A transmission electron microscopy study. Water Research 45 (1): 179-190
- McLachlan M, Czub G, MacLoad M, Arnot JA 2011. Bioaccumulation of organic contaminants in humans: a multimedia perspective and the importance of biotransformation. Env. Sci. Technol. 45 (1): 197–202
- Ng CA, Scheringer M, Fenner K, Hungerbuhler K 2011. A framework for evaluating the contribution of transformation products to chemical persistence in the environment. Env. Sci. Technol. 45 (1): 111–117
- Nendza M, Müller M 2010. A Screening for low aquatic bioaccumulation (1): Lipinski's 'Rule of 5' and molecular size. SAR and QSAR in Environmental Research 21 (5&6): 495-512
- Schwöbel JAH, Wondrousch D, Koleva YK, Madden JC, Cronin MTD, Schüürmann G 2010. Prediction of Michael-type acceptor reactivity toward glutathione. Chem. Res. Toxicol. 23 (10): 1576-1585
- Yu H, Kühne R, Ebert R-U, Schüürmann G 2010. Comparative analysis of QSAR models for predicting pKa of organic oxygen acids and nitrogen bases from molecular structure. SAR and J. Chem. Inf. Model. 50 (11): 1949-1960
- Böhme A, Thaens D, Schramm F, Paschke A, Schüürmann G 2010. Thiol reactivity and its impact on the ciliate toxicity of a,ß-unsaturated aldehydes, ketones, and esters. Chem. Res. Toxicol. 23 (12): 1905–1912
- Blaschke U, Paschke A, Rensch I, Schüürmann G 2010. Acute and chronic toxicity toward the bacteria *Vibrio fischeri* of organic narcotics and epoxides – Structural alerts for epoxide excess toxicity. Chem. Res. Toxicol. 23 (12): 1936–1946
- Schäfer RB, Pettigrove V, Rose G, Allinson G, Wightwick A, von der Ohe PC, Shimeta J, Kühne R, Kefford BJ 2011. Effects of pesticides monitored with three sampling methods in 24 sites on macroinvertebrates and microorganisms. Environ. Sci. Technol. 45 (4): 1665-1672
- 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, in press, available online

Book Articles

- Klinke A, Renn O 2010. Risk Governance: contemporary and future challenges. In: Eriksson J, Gilek M, Rudén C (eds): Regulating chemical risks. European and global challenges. Springer, Dordrecht, pp. 9-28

- Cronin MTD, Madden JC (eds): In Silico Toxicology: Principles and Applications, Royal Society of Chemistry, Cambridge, UK
  - Cronin MTD, Madden JC 2010. In silico toxicology – An introduction. pp. 1-10
  - Madden JC 2010. Introduction to QSAR and other in silico methods to predict toxicity. pp. 11-30
  - Cronin MTD 2010. Finding the data to develop and evaluate (Q)SARs and populate categories for toxicity prediction. pp. 31-58
  - Nendza M, Aldenberg T, Benfenati E, Benigni R, Cronin M, Escher S, Fernandez A, Gabbert S, Giralt F, Hewitt M, Hrovat M, Jeram S, Kroese D, Madden J, Mangelsdorf I, Rallo R, Roncaglioni A, Rorije E, Segner H, Simon-Hettich B, Vermeire T 2010. Data quality assessment for in silico methods: A survey of approaches and needs. pp. 59-107

* Cronin MTD 2010. Characterisation, evaluation and possible validation of in silico models for toxicity: determining if a prediction is valid. pp. 275-300
* Hewitt M, Ellison CE 2010. Developing the applicability domain of in silico models: relevance, importance and methodology. pp. 301-333
* Cronin MTD 2010. Biological read-across: mechanistically-based species-species and endpoint-endpoint extrapolations. pp. 446-477
* Madden JC 2010. Toxicokinetic considerations in predicting toxicity. pp. 531-557
* Aldenberg T, Jaworska JS 2010. Multiple test in silico Weight-of-Evidence for toxicological endpoints. pp. 558-583

In Silico Toxicology: Principles and Applications

Key findings and progress from the OSIRIS project have formed the basis of a new book entitled "*In Silico* Toxicology: Principles and Applications". The book is an informative text that describes the development and use of (quantitative) structure-activity relationships ((Q)SARs) and category formation allowing for read-across for the prediction of toxicity and fate. It emphasises how such predictions can be used in a regulatory context.

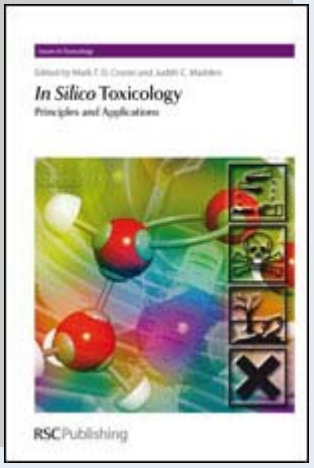
The book was edited by Mark Cronin and Judith Madden (Liverpool John Moores University) and leads the reader through every aspect of developing and using *in silico* models. The volume is set out logically starting with the philosophy and history of modelling. This is complemented by a description of the types of existing toxicity data that may be obtained and utilised both to assess the hazard of a particular compound and also for model building. This builds upon the expertise and knowledge gained from the OSIRIS project. A particular outcome of the OSIRIS project is seen in a multiauthor chapter that describes how to assess data quality, reviewing both the state of the art and making recommendations for the future.

Following on from the sourcing of data a number of chapters lead the reader through the types and calculation of physico-chemical properties and structural descriptors, such that are useful in predictive toxicology. These range from property estimation, through 2-D descriptors to the use of 3-D properties for the assessment of receptor binding relating to toxicological effects. This is supported by didactic chapters relating to appropriate statistical analysis for both continuous and categoric data.

Two chapters build on work from the OSIRIS project with regard to regulatory use of (Q)SAR predictions. The first of these provides an overview into the characterisation, evaluation and possible validation of (Q)SARs for possible regulatory use. The second describes methods that can be used to assign and utilise the applicability domain of a model.

There is also a particular emphasis on the existing tools that are used to predict toxicity including popular expert systems, the OECD (Q)SAR Toolbox and freely available software for modelling purposes. The final chapters draw upon expertise in developing categories for read-across as well as integrated testing strategies weight of evidence approaches and the illustration of the use of predictive methods with case studies. Findings from the OSIRIS project feature here with a description of the role of toxicokinetics in the prediction of harmful effects as well as use of weight of evidence (Bayesian approaches).

Overall the book illustrates the importance of the OSIRIS project in promoting fundamental tools and approaches for toxicity prediction. It sets out a logical workflow from collecting data, calculation of descriptors, model development, interpretation of the model through to integration of predictions with other information.



Cronin MTD, Madden JC (eds): *In Silico* Toxicology: Principles and Applications, RSC Publishing, Cambridge, UK

Available from: http://www.rsc.org/shop/books/2010/9781849730044.asp.

Single chapters are also available for purchase as a pdf file.

OSIRIS ITS Stakeholder Workshop: Programme

The next **OSIRIS Stakeholder Workshop** on Integrated Testing Strategies (ITS) will be held

on **Tuesday 8 March – Wednesday 9 March 2011**

at the Helmholtz Centre for Environmental Research – UFZ in **Leipzig**, Germany.

Key stakeholders and experts from regulatory authorities, industry and academia are invited to test the methods and ITS developed within OSIRIS. The feedback for the final phase of the project will be highly appreciated.

OSIRIS is developing Integrated Testing Strategies considering both non-test and test information and thus combining different approaches for the hazard and risk evaluation of chemicals.

The methods and ITS developed are implemented in the webbased OSIRIS Tool, which will be made available to the public at the end of the project.

The Workshop addresses the ITS implemented in the OSIRIS Webtool for the following **endpoints**:

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

The ITS presentation and discussion will include:

- Background information on the ITS
- Demonstration of the ITS Webtool with concrete examples
- Practical application and exercise
- Feedback.

Registration is possible for the whole workshop or for specific endpoint sessions via email to **osiris-workshop@ufz.de**.

More information on the workshop, the venue and registration is available at **www.osiris-reach.eu**.

Programme

Tuesday 8 March 2011

8.00 – 9.00	Registration and check of the software implementation on participants' laptops	
INTRODUCTION		
9.00 – 9.30	Welcome Introduction on OSIRIS and ITS	Gerrit Schüürmann, UFZ
9.30 – 9.45	Demo of the OSIRIS Webtool	Eduard Pauné, SIMPPLE
SKIN SENSITISATION		
9.45 – 10.30	Background REACH requirements, ITS Introduction skin sensitisation ITS webtool	Emiel Rorije, RIVM Tom Aldenberg, RIVM
10.30 – 11.00	Coffee Break	
11.00 – 12.45	Demo of skin sensitisation ITS webtool with concrete examples Practical application including exercises by participants	Emiel Rorije, RIVM Tom Aldenberg, RIVM
12.45 – 13.15	Feedback: skin sensitisation ITS (questionnaire distributed in addition)	Emiel Rorije, RIVM Tom Aldenberg, RIVM
13.15 – 14.15	Lunch Break	
REPEATED DOSE TOXICITY		
14.15 – 15.00	Background REACH requirements, ITS Introduction repeated dose toxicity webtool	Sylvia Escher, FhG Inga Tluczkiewicz, FhG
15.00 – 16.00	Demo of repeated dose toxicity ITS webtool with concrete examples Practical application including exercises by participants	Sylvia Escher, FhG Inga Tluczkiewicz, FhG
16.00 – 16.30	Coffee Break	
16.30 – 17.15	Demo of repeated dose toxicity ITS webtool with concrete examples Practical application including exercises by participants (continued)	Sylvia Escher, FhG Inga Tluczkiewicz, FhG
17.15 – 17.45	Feedback: repeated dose toxicity ITS (questionnaire distributed in addition)	Sylvia Escher, FhG Inga Tluczkiewicz, FhG
19:00	Dinner	

Wednesday 9 March 2011

8.00 – 9.00	Registration and check of the software implementation on participants' laptops	
BIOCONCENTRATION FACTOR		
9.00 – 9.45	Background REACH requirements, ITS Introduction BCF webtool	Monika Nendza, AL Alessandra Roncaglioni, IRFMN
9.45 – 10.30	Demo of BCF ITS webtool with concrete examples Practical application including exercises by participants	Anna Lombardo, IRFMN Alessandra Roncaglioni, IRFMN
10.30 – 11.00	Coffee Break	
11.00 – 12.00	Demo of BCF ITS webtool with concrete examples Practical application including exercises by participants (continued)	Anna Lombardo, IRFMN Alessandra Roncaglioni, IRFMN
12.00 – 12.30	Feedback: BCF ITS (questionnaire distributed in addition)	Anna Lombardo, IRFMN Alessandra Roncaglioni, IRFMN
12.30 – 13.30	Lunch Break	
AQUATIC TOXICITY		
13.30 – 14.00	Background REACH requirements, ITS	Alessandra Roncaglioni, IRFMN Anna Lombardo, IRFMN
14.00 – 15.00	Introduction aquatic toxicity webtool and associated ITS workflow	Anna Lombardo, IRFMN Alessandra Roncaglioni, IRFMN
15.00 – 15.15	Feedback: aquatic toxicity ITS (questionnaire distributed in addition)	Alessandra Roncaglioni, IRFMN Anna Lombardo, IRFMN
15.15 – 15.45	Coffee Break	
MUTAGENICITY & CARCINOGENICITY		
15.45 – 16.15	Background REACH requirements, ITS	Dinant Kroese, TNO Emiel Rorije, RIVM
16.15 – 17.15	Introduction mutagenicity & carcinogenicity webtool and associated ITS workflow	Dinant Kroese, TNO Emiel Rorije, RIVM
17.15 – 17.30	Feedback: mutagenicity & carcinogenicity ITS (questionnaire distributed in addition)	Dinant Kroese, TNO Emiel Rorije, RIVM

Conference Calendar: OSIRIS-related Events

Third International Conference on Alternatives for Developmental Neurotoxicity Testing (DNT3)
10 – 13 May 2011, Ville Ponti Congress Centre, Varese, Italy
http://ihcp.jrc.ec.europa.eu/events_workshops/dnt3conference

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
http://www.cityu.edu.hk/bch/ista15/

Micropol & Ecohazard 2011
11 – 13 July 2011, Sydney, Australia
7th IWA specialist conference on assessment and control of micropollutants/hazardous substances in water
http://micropol2011.org/

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/

EmCon2011 – 3rd International Conference on Occurrence, Fate, Effects, and Analysis of Emerging Contaminants in the Environment
23 – 26 August 2011, Copenhagen, Denmark
http://www.emcon2011.com/

EUROTOX 2011
28 – 31 August 2011, Paris, France
http://www.eurotox2011.com/site/-Homepage,1551-

CMTPI-2011 – 6th International Symposium on Computational Methods in Toxicology and Pharmacology Integrating Internet Resources
3 – 7 September 2011, Maribor, Slovenia
http://cmtpi-2011.si/

ICCE 2011 - 13th EuCheMS International Conference on Chemistry and the Environment
11 – 15 September 2011, Zurich, Switzerland
Emerging Issues in Environmental Chemistry: from Basic Research to Implementation
European Association for Chemical and Molecular Sciences
http://www.icce2011.org

The conference list with a preview of more 2012 conferences is also available at:

www.osiris-reach.eu > Events and Activities

Conference Calendar: OSIRIS-related Events

SETAC-GLB Meeting
18 – 20 September 2011, Landau, Germany
Society of Environmental Toxicology and Chemistry Europe German Language Branch
http://www.setac-glb.de/

SETAC North America 32nd Annual Meeting
13 – 17 November 2011, Boston, MA, USA
http://www.setac.org/node/7

6th SETAC World Congress
20 – 24 May 2012, Berlin, Germany
http://www.setac.org/node/7

EUROTOX 2012
17 – 20 June 2012, Stockholm, Sweden
http://www.eurotox2012.org/

Final OSIRIS Meeting

The Final OSIRIS Meeting will be held
on 27 – 29 September 2011
in Leipzig, Germany
at the Helmholtz Centre for Environmental Research – UFZ, hosted by the OSIRIS Coordinator UFZ.

Photos: Andrea Richarz

The Final Meeting will include the final OSIRIS General Assembly meeting and the final dissemination event:

The results obtained within OSIRIS will be presented and the final version of the OSIRIS Integrated Testing Strategies (ITS) Webtool will be demonstrated to Stakeholders.

Responsible for the OSIRIS Newsletter : Dr. Andrea Richarz
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SIXTH FRAMEWORK PROGRAMME