OSIRIS Training Course

MILAN • Italy • 23-25 September 2009

DESCRIPTION

PROGRAMME

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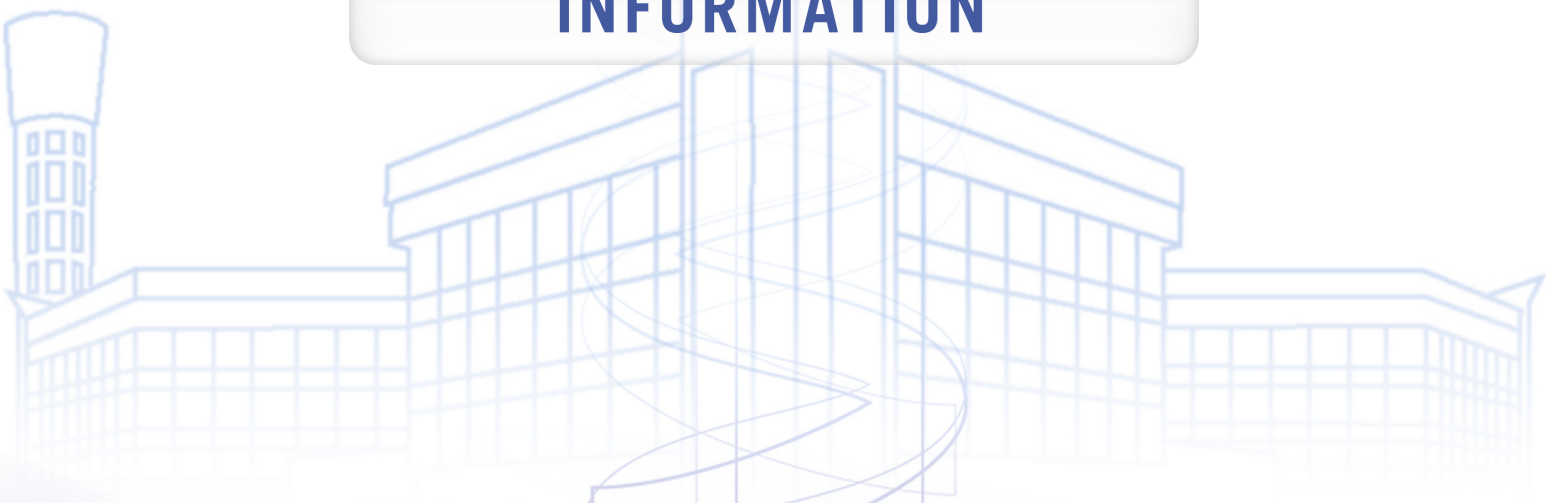
INFORMATION



MARIO NEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

Description

The second *OSIRIS Training Course on Integrated Testing Strategies (ITS)* will be held in Milan, Italy, on 23-25 September 2009.

The Course will address risk assessment under 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.

The Course is constituted by *two modules*: the first one is a *theoretical introduction to risk assessment* and will also provide the necessary background to the software and tools to be used for the second module, devoted to *practical case studies*.

The following *speakers* will take part in the Course:

Emilio Benfenati - Mario Negri Institute (IRFMN), Italy
Kees van Leeuwen - TNO, The Netherlands
Theo Vermeire - RIVM, The Netherlands
Yuri Bruinen de Bruin - RIVM, The Netherlands
Silke Gabbert - Wageningen University (WUR), The Netherlands
Romualdo Benigni - Istituto Superiore di Sanità (ISS), Italy
Mark Cronin - Liverpool John Moores University (LJMU), UK
Andrew Worth - EC Joint Research Centre (EC JRC), Italy
Arianna Bassan - S-IN Soluzioni Informatiche, Italy
Andrea Richarz - UFZ, Germany
Eduard Pauné - SIMPPLE, Spain

Module 1

CONCEPTUAL BACKGROUND

23 September, 14:00 - 17:50
Room C - Alfredo Leonardi - 1st floor

13:30	REGISTRATION OPENING - IRFMN Reception

TIME	PRESENTATION TITLE	SPEAKER & AFFILIATION
14:00	Welcome and Introduction	Emilio Benfenati - IRFMN
14:10	Introduction to Risk Assessment	Kees van Leeuwen - TNO Theo Vermeire - RIVM
15:00	REACH Procedures and the Chemical Safety Assessment	Yuri Bruinen de Bruin - RIVM
15:50	COFFEE BREAK (30 minutes)	
16:20	Integrated Testing Strategies for REACH	Kees van Leuwen - TNO
17:00	Introduction to Cost-effectiveness Analysis	Silke Gabbert - WUR

24 September, 09:00 - 13:00
Room C - Alfredo Leonardi - 1st floor

08:30	REGISTRATION OPENING - IRFMN Reception

TIME	PRESENTATION TITLE	SPEAKER & AFFILIATION
09:00	Endpoint-specific Background for Web Tool Demonstration on BCF	Emilio Benfenati - IRFMN
09:50	Developing Strategies for *in vitro*, *in vivo* and *in silico* Information in Mutagenicity/Carcinogenicity	Romualdo Benigni - ISS
10:40	COFFEE BREAK (30 minutes)	
11:20	Mode-of-Action Framework for Toxicity Prediction: Concepts and Use of Information	Mark Cronin - LJMU
12:10	Reporting Formats for QSARs: QMRF, QPRF	Andrew Worth - EC JRC
13:00	LUNCH	

Module 2

DEMONSTRATIONS & PRACTICAL CASE STUDIES

24 September, 14:30 - 18:00
Educational Room at the IRFMN Residence

TIME	PRESENTATION TITLE	SPEAKER & AFFILIATION
14:30	Case Studies using Software Tools for Profiling Chemicals and Generating Predictions of Toxicity (including *CAESAR Toxicity Prediction Models*, *Toxtree and OECD (Q)SAR Application Toolbox*)	Multiple *demonstrators* including: Emilo Benfenati - IRFMN Arianna Bassan - S-IN Mark Cronin - LJMU
15:30	COFFEE BREAK (30 minutes, comprised within Case Studies session)	
17:00	A Collection of *in silico* Tools for Generating Non-testing Data for Chemical Hazard Assessment	Arianna Bassan - S-IN

25 September, 09:00 - 12:30
Educational Room at the IRFMN Residence

08:30	REGISTRATION OPENING - IRFMN Reception

TIME	PRESENTATION TITLE	SPEAKER & AFFILIATION
09:00	Discussion on Adequacy of Non-Testing Information	ROUNDTABLE *Moderator*: T.B.A.
10:15	COFFEE BREAK (30 minutes)	
10:45	Demonstration of ChemProp - Chemical Properties Estimation Software System	Andrea Richarz - UFZ
11:35	Demonstration of OSIRIS Web Tool	Eduard Pauné - SIMPPLE

Brief Information

Due to internal regulations of the Mario Negri Institute for Pharmacological Research (IRFMN), which hosts the Course, all participants will be asked to sign a specific *registration form* at the entrance and before leaving at the end of each day.

Concerning *timetable*, each speaker will have at least 50 minutes, including 40 minutes for presentation and 10 minutes devoted to questions and discussion.

Abstracts

Introduction to Risk Assessment

Kees van Leuwen (TNO) and Theo Vermeire (RIVM)

This introduction will first of all explain the role of risk assessment (RA) in the control of chemicals and its relation with risk management (RM). Major frameworks for RA-RM will be shown. The focus will be on industrial chemicals and REACH. The risk assessment endpoints covered are risks to the environment and three human populations: consumers, workers and humans exposed via the environment. Each of the basic elements of RA will be defined and explained: hazard assessment and dose-response evaluation, exposure assessment and risk characterisation. Data evaluation, data needs, methodology and output for each of these steps are discussed as well as available tools. Special attention will be given to the role of the exposure scenario in the chemical safety assessment under REACH, risk characterisation and the way uncertainty and variability in scenarios, models, and parameters can be approached. Finally, the meaning of the lessons learned for decision making will be discussed.

REACH Procedures and the Chemical Safety Assessment

Yuri Bruinen de Bruin (RIVM)

For a good understanding of REACH procedures first of all a brief overview of the events leading up to the Regulation will be presented. Next the aim and the general aspects of REACH will be explained including registration, evaluation, authorization, restriction, data requirements, data sharing, testing strategies, the available guidance and tools. A central element of REACH is the Chemicals Safety Assessment (CSA). Its aim, scope and important steps will be explained as well as how the Chemical Safety Assessment should be prepared and how the output should look like. The lecture will end with an impression of the experience gained so far and with a discussion.

Integrated Testing Strategies for REACH

Kees van Leuwen (TNO)

Integrated Testing Strategies (ITS) are carefully designed approaches for combining the use of different testing and non-testing methods (including QSARs) in an optimal manner, in order to: a) increase the efficiency and effectiveness of hazard and risk assessments; b) minimise costs; and c) reduce, replace and refine animal testing to the extent possible, while at the same time ensuring a sufficient protection of human and environmental health.

A general principle is that the need for additional testing should be limited to obtaining only essential information, rather than testing "unintelligently" and to cover all data gaps according to an indiscriminate checklist approach. Thus, testing is focused on chemicals and properties of concern, and properties that are expected to influence the regulatory decision. Many ITS have been proposed in the scientific literature, and some have been agreed at the regulatory level for the implementation of REACH. This presentation explains the conceptual basis of ITS, and provides illustrations of how the different component parts of ITS (e.g. QSARs and in vitro tests) can be combined to provide the information needed for hazard and risk assessment. The opportunities and challenges posted by ITS are also emphasised.

Introduction to Cost-effectiveness Analysys

Silke Gabbert (WUR)

Cost-effectiveness analysis (CEA) provides a consistent and systematic economic framework for assessing the performance of programmes or interventions according to effects and costs. The objectives of the lecture are: a) to give an introduction to the cost-effectiveness analysis method; b) to illustrate how CEA can be used for assessing the performance of chemical tests and testing strategies; c) to discuss how CEA can be applied as a decision-support tool, providing guidance on how to optimally allocate scarce resources on a set of alternative chemical tests and testing strategies.

The lecture will be divided into two parts. The first part focuses on methodological and theoretical aspects of CEA, explaining the economic foundations of CEA, its strengths and limitations, and how it is related to other cost-analysis methods such as, for example, cost-benefit analysis. In the second part of the lecture we illustrate how CEA can be applied for an economic evaluation of chemical tests and testing strategies to be used for regulatory purpose.

Endpoint-specific Background for Web Tool Demonstration on BCF

Emilio Benfenati (IRFMN)

Information about bioaccumulation is very important for REACH within the context of PBT assessment and classification and labelling. Depending on the tonnage a classification is sufficient, or a continuous value may be requested, for risk assessment. For a rapid evaluation of the bioconcentration factor (BCF) as a category, log P value has been suggested, which is the partition coefficient between octanol and water, given as a logarithm. Several thresholds have been proposed. As a way to assist evaluation of BCF, both as classifier and as a continuous value, other tools have been proposed. The project CAESAR produced several models. The advantage is that it is possible to have both a category and a continuous value, no experiment is necessary, not even to measure logP, and an applicability domain can be defined. EPI Suite developed new software for this. In the literature there are several models. This presentation will compare results between the different methods and discuss this topic in the framework of the ITS.

Developing Strategies for *in vitro*, *in vivo* and *in silico* Information in Mutagenicity/Carcinogenicity

Romualdo Benigni (ISS)

In vivo mutagenicity studies, shortly followed by carcinogenicity, pose high demand for test-related recourses: therefore, the development and use of estimation techniques such as (Q)SARs, read-across and grouping of chemicals, might have a huge saving potential for these endpoints. Structure-Activity Relationships paradigm provides a wide range of tools. Some are coarse-grain approaches such as Structural Alerts (SA): these have a crucial role in risk assessment, for: a) description of sets of chemicals; b) preliminary hazard characterization; c) formation of categories; d) generation of subsets of congeneric chemicals to be analyzed subsequently with quantitative (QSAR) methods; e) priority setting . On the other side, there are fine-tuned QSARs for congeneric classes of chemicals. Good quality, local QSARs for mutagenicity and carcinogenicity, when challenged for their predictivity in respect to real external test sets were 70 to 100 % correct in their external predictions. A crucial issue is that of the uncertainty of the modeling approaches. More properly, their uncertainty should be compared with that of the competing experimental tests. For example, the ability of SAs to predict rodent carcinogenicity is of the same order of the Ames test (around 65% accuracy). Equally illuminating is the fact that the external predictivity of good local QSARs (70 to 100 % accuracy) is of the same order of the reported inter-laboratory variability of the Ames test (85%). Thus, uncertainties are proper to both modeling and experimental systems. The crucial issue is that of exploiting and combining –at their best- both methods.

Mode-of-Action Framework for Toxicity Prediction: Concepts and Use of Information

Mark Cronin (LJMU)

There are numerous opportunities to use information relating to mode and mechanism of toxic action in integrated testing strategies. Definition of the terms (mode and mechanism of action) is possible, but is often open to debate and interpretation – particularly between the human health and environmental areas. The use of information from modes and mechanisms can be applied to identify the correct QSAR for use. In addition, grouping compounds by mode and/or mechanism of action will assist in the development of categories to enable read-across for toxicity prediction. All these approaches may result in a reduction of in vivo testing on organisms. In addition, they allow for the combination of available data on a mode of action and a focus on the potentially most toxic groups.

These approaches are appropriate for both human health and environmental endpoints. Different approaches can be used dependent on the endpoint. Approaches to assign a chemical to a particular mode or mechanism of action can be summarised as belonging to one or more of the following:

- Chemical and / or structural features;
- (Q)SARs incorporating physicochemical properties;
- Molecular, chemical and / or biological responses such as receptor binding, mutagenicity and possibly -omics;
- Integrative/apical biological responses such as lethality etc.

Different techniques to determine mechanisms of action and possible uses will be outlined with examples in this presentation.

Reporting Formats for QSARs: QMRF, QPRF

Andrew Worth (EC JRC)

In the regulatory assessment of chemicals (e.g. under REACH), (Q)SAR models are playing an increasingly important role in predicting properties for hazard and risk assessment. This implies both a need to be able to identify relevant (Q)SARs and to use them to derive estimates and/or have access to their pre-calculated estimates.

The QSAR Model Reporting Format (QMRF) is a harmonised template for summarising and reporting key information on (Q)SAR models, including the results of any validation studies. The information is structured according to the OECD (Q)SAR validation principles.

The QSAR Prediction Reporting Format (QPRF) is a harmonised template for summarising and reporting substance-specific predictions generated by (Q)SAR models.

Case Studies using Software Tools for Profiling Chemicals and Generating Predictions of Toxicity (including CAESAR Toxicity Prediction Models, Toxtree and OECD (Q)SAR Application Toolbox)

Multiple demonstrators including Emilio Benfenati (IRFMN), Arianna Bassan (S-IN Soluzioni Informatiche) and Mark Cronin (LJMU)

A number of case studies, using REACH-relevant chemicals, will be provided. These will include demonstrations and the possibilities for hands-on use of new software including:

- CAESAR Models for Toxicity Prediction
- Toxtree
- OECD (Q)SAR Application Toolbox

The case studies will demonstrate how these computational tools can be used to make predictions of toxicity as well as profiling chemicals to allow for their grouping into categories. Examples of how read-across could be provided from tools categories will be provided. The case studies will highlight how these tools can be used successfully and the pitfalls to avoid.

A Collection of *in silico* Tools for Generating Non-testing Data for Chemical Hazard Assessment

Arianna Bassan (S-IN Soluzioni Informatiche)

To limit the cost and the number of animals used for testing, REACH explicitly encourages the use of computer-aided methods such as (Q)SAR methods and category/read-across approaches for filling in the enormous knowledge gap of chemical information. In this training session, the following topics will be presented and discussed:

- Review of computational tools for applying (Q)SARs.
- Reporting Formats (e.g. QSAR Model Reporting Format, QMRF) for providing adequate documentation about the models.
- Structured workflow that assists users all the way through the generation of reliable non-testing data and by aiding the following processes: (a) retrieving existing physico-chemical properties and (eco)toxicological information for a given chemical; (b) selecting relevant in silico approaches for predicting individual toxic endpoints; (c) generating endpoint predictions; (d) providing information on the reliability of the estimates; (e) exploiting the capability of various in silico methodologies; (f) integrating results and (g) compiling robust summaries that document in a transparent way the use of the methods.
- Hands-on session on a number of tools and applications (e.g., ACD Labs, Pharma Algorithms, DSSTox, KNIME).

Demonstration of ChemProp

Andrea Richarz (UFZ)

ChemProp (*Chemical Properties Estimation Software System*) is a software system developed at the UFZ Department of Ecological Chemistry that enables automated chemical structure and substructure searching and calculation of compound properties. Implemented models cover physical-chemical properties with a particular focus on partitioning between and degradation in environmental compartments, standard Mackay-type fate simulation, and ecotoxicological as well as human toxicological endpoints. Quantitative models include fragment methods, Abraham models and property-property-relationships, and qualitative models cover structural alert approaches for various endpoints. The implemented techniques are usually based on 2D structures including an automated substructure search. The calculation models have access to the internal databases providing a number of experimental properties. ChemProp also offers basic statistical analyses including respective plots and compound class specific analyses. Particular remark is given to the model applicability domain. As long as the necessary information can be extracted from the respective literature sources, an automated control on domain coverage during estimation runs is included. The chemical domain is addressed by atom-centred fragments (ACFs). The database enables full structure and substructure searching besides and in combination with queries via name, molecular formula, registry number, InChI, and properties. Also, access to web resources is supported via the chemical structure. The database currently contains about 15,000 structures. Moreover, there is a module for the access to external SQL compatible ODBC sources, allowing for the inclusion of almost any relational third-party databases and thus enabling to maintain complex data structures and to apply the full strength of structure and substructure searching to them. The use of ChemProp will be demonstrated with several examples.

Demonstration of OSIRIS Web Tool

Eduard Pauné (SIMPPLE)

The demonstration will start with a short description of the main goals of the OSIRIS ITS web tool, and the most relevant features.

After the introduction, the practical use of the tool will be demonstrated: several substances will be introduced in the tool, and data (test, non-test and physicochemical) will be added to the substances, using the different mechanisms that the tool provides (direct input, database connectivity and data from IUCLID5).

Several endpoints will be assessed on the substances, demonstrating the execution of assessments and the introduction of expert judgements.

Course Fee & Costs

Participation into the OSIRIS Training Course is ***FREE*** and ***no fee*** has to be paid for registration.

Travel and living expenses have to be charged directly by each participant, with the exception of costs for coffee breaks and lunch during the course sessions, which will be paid by the local organization.

Registration

In order to apply for the OSIRIS Training Course please send an e-mail to the address:

osiris.training@marionegri.it

specifying the following details:

Surname and Name

Affiliation

Selected Module *(Module 1, Module 2 or both)*

Participation is free, depending on a limited availability of places.
For this reason, early registrations will be favoured.

In addition, multiple applications from the same organization/laboratory will be disfavoured.

DEADLINE *for registration is* ***15 August 2009***

Applicants will be notified about acceptance or rejection at the latest within *20 August 2009*.

Cont@cts

To get information about the *OSIRIS Training Course*, the *venue* and *local arrangements* you can refer to the following contacts:

e-mail: *osiris.training@marionegri.it*
phone: *+39-02-3901.4394 /.4595/.4396*
fax: *+39-02-3901.4735*

Venue

Milano

MARIO NEGRI INSTITUTE FOR PHARMACOLOGICAL RESEARCH

Via Giuseppe La Masa, 19
20156 MILAN Italy
http://www.marionegri.it

information

HOW TO GET TO THE COURSE VENUE

Milan is easily reachable from *three international airports*: **Milano Linate** (near to the downtown, at about 12 km from Mario Negri Institute), **Milano Malpensa** (40 km) and **Milano Orio al Serio** (50 km, near to Bergamo):

- **From Milano Linate:** you can use taxi or bus until Piazza San Babila, in the centre of Milan, where you can take the subway Linea 1 to the railway station Cadorna Ferrovie Nord: every train starting from Cadorna station stops at the Milano Bovisa Politecnico station, very close to Mario Negri Institute (*see below*).
- **From Milano Orio al Serio:** there is a shuttle bus to the railway station Milano Centrale, from where you can use the subway Linea 2 to get the station Cadorna Ferrovie Nord and then, by train, the Mario Negri Institute (*see below*).
- **From Milano Malpensa:** you can take the train called Malpensa Express to the downtown: this is the simplest solution because Malpensa Express stops at the aforementioned station Milano Bovisa Politecnico, near to Mario Negri Institute.
- **If you already are in Milan**, the easiest way to get Mario Negri Institute is taking a train from Cadorna Station: every train starting from Cadorna Station stops at the station Milano Bovisa Politecnico, very close to Mario Negri Institute.

ACCOMMODATION & TRANSPORTS IN MILAN

Detailed information about ACCOMMODATION and TRANSPORTS in Milan is available at the following web page:

http://www.insilico.eu/pages_en/info01.html

including an interactive map of the Mario Negri Institute area, a list of suitable hotels (with contacts and indicative prices), a series of maps for transport service and useful links.