

TRISK

European Toxicology Risk Assessment Training Programme

2010-2011

The European Toxicology Risk Assessment Training Programme is organised by TRISK, a project that is funded by the European Union, in the framework of the Second Programme of Community Action in the field of Health (2008-2013).

Five European universities and one research consortium are partners in the TRISK project:

University of Milan, Italy
University of Surrey, UK
Karolinska Institutet, Sweden
University of Düsseldorf, Germany
University of Utrecht, The Netherlands
Technoalimenti SCpA, Italy.

The objective of the training programme is to provide a comprehensive training in toxicological risk assessment that serves as a model for future European training in risk assessment for accredited European risk assessors.

The training programme is intended for individuals who have previous training or experience in toxicology and who would like to pursue a career in risk assessment in Europe in industry, regulatory authorities, consultancy or academia.

The intended learning outcome

After successfully completing the training programme the trainee should be able to

- understand and describe the risk assessment procedure including the different steps involved
- identify sources to obtain data needed for a risk assessment
- analyse and evaluate data to be used for risk assessment
- identify data gaps and suggest additional studies
- critically evaluate risk assessment documents
- conduct a full risk assessment
- understand and describe different regulatory frameworks
- understand the role of risk communication

The training programme includes eight 1-week-long course modules, an applied training at an institution performing risk assessments and a final examination.

		2010												2011											
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Eight course modules	8 x 1 week																								
Applied training	450 hours																								
Final examination	1 day																								

Course modules

Module	Content	Time	Location
Module 1	Introduction to risk assessment and management, with special attention to chemical risk assessment	February 1-5, 2010	Karolinska Institutet, Stockholm, Sweden
Module 2	Role of ADME in risk assessment	March 8-12, 2010	University of Surrey, Guildford, UK
Module 3	Identification and assessment of genotoxic and non-genotoxic carcinogens	June 14-18, 2010	University of Milan, Italy
Module 4	Exposure analysis in risk assessment	July 5-9, 2010	University of Utrecht, Netherlands
Module 5	Identification and assessment of organ toxicity, including neurotoxicity, immunotoxicity	September 20-24, 2010	University of Düsseldorf, Germany
Module 6	Epidemiology and statistics in toxicological risk assessment	November 8-10, 2010	University of Utrecht, Netherlands
Module 7	Identification and assessment of reproductive toxicity and endocrine disruption	January 31-February 4, 2011	Karolinska Institutet, Stockholm, Sweden
Module 8	Supplementary module. Any other suitable course available in Europe on a specific aspect of risk assessment such as cosmetics, plant protection products and biocides, consumer products, medicines and veterinary drugs, contaminants in food, soil and water, industrial chemicals, occupational exposure, risk communication, 3Rs in risk assessment.	January 2010-November 2011	Different organisers

Participation in some course modules can be waived if the trainee has previously obtained the knowledge and skills addressed in the module.

Module 1: Introduction to risk assessment and management, with special attention to chemical risk assessment

Module leaders:

Assoc prof Annika Hanberg, Dr Mattias Öberg and Prof Helen Håkansson, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Content:

The course module will include fundamental concepts in toxicology, epidemiology, exposure and risk assessment, and will also cover risk assessment and risk management in regulatory decision-making. Standardized test guidelines and GLP will be covered. Attention will be paid to interpretation possibilities and evaluation of data from different test systems, handling of uncertainties and data gaps, and other critical issues in health risk assessment. Particular focus will be given to identification of critical effects, extrapolation to humans and sensitive groups, application of assessment factors and allocation of health-based guidance values. Specific risk assessments of problematic chemicals will be discussed.

- Concepts in toxicology and risk analysis
- Standardized test guidelines, testing strategies and GLP
- Web-based information sources in toxicology and risk assessment, including a computer-based exercise
- Epidemiological principles, interpretation of results in epidemiology
- Introduction to exposure assessment
- Assessment of effect data (QSAR, *in vitro*, *in vivo*, epidemiology)
- Introduction to standard setting
- Classification and labelling
- Risk perception, risk communication and risk management
- Risk assessment of chemicals in Europe, REACH and ECHA
- Risk assessment and food safety, EFSA
- European procedure for occupational exposure limits, SCOEL
- Examples of problematic risk assessment (e.g. Dioxin, trichloroethylene, PFOS, cadmium)
- Group work on exposure assessment, hazard characterization and risk characterization

Learning outcomes:

- a general knowledge and understanding of the methods and procedures used in health risk assessment.
- a professional attitude towards the complexity in interpretation of toxicological and epidemiological studies for use in health risk assessment.

Module 2: Role of ADME in risk assessment

Module leader:

Dr Shirley Price, Division of Biochemical Sciences, Faculty of Health and Medical Sciences, University of Surrey, UK

Content:

A good knowledge of the principles of xenobiotic metabolism is central to toxicology because many compounds undergo enzymic metabolism to form toxic metabolites. Similarly, many toxicants are inactivated by the action of xenobiotic metabolising enzymes. Toxicokinetics is the study of the rates of absorption, distribution, metabolism and excretion of toxicants, and is central to an understanding of the exposure of target tissues to toxicants. This module focuses on toxicokinetics and xenobiotic metabolism with particular emphasis on risk assessment. It also covers an overview of lung, oral and intestinal absorption; metabolism – phases I and II; skin absorption and metabolism; stereoselectivity in drug metabolism and toxicology; enzymology and molecular biology; distribution and excretion; toxicodynamic effects, reactive molecules and dose response curves; basic xenobiotic metabolism and the implications for drug development; techniques for measuring xenobiotics; plasma monitoring for therapeutic optimisation; basic pharmacokinetics; bioavailability; interspecies comparison in drug metabolism and toxicokinetics; extrapolation of data from animals to man; and pharmacokinetic modelling. These concepts will be illustrated throughout by 'real world' examples.

- Overview: lung, oral and intestinal absorption
- Metabolism - Phase I and II
- Skin absorption and metabolism
- Stereoselectivity in drug metabolism and toxicology
- Enzymology and molecular biology
- Distribution and excretion
- Toxicodynamic effects, reactive molecules and dose-response curves
- Basic xenobiotic metabolism and the implications for drug development
- Techniques for measuring xenobiotics
- Plasma monitoring for therapeutic optimisation
- Basic pharmacokinetics
- Bioavailability
- Interspecies comparison in drug metabolism and toxicokinetics
- Extrapolation of data from animals to man
- Pharmacokinetic modelling
- Case studies on the importance of metabolism in interpreting toxicity data and in deriving uncertainty factors
- Case study on the use of toxicokinetic models in route-to-route and interspecies extrapolation

Learning outcomes:

- understand the importance of metabolism and toxicokinetics in the interpretation of toxicity data and in quantitative risk assessment
- understand the major pathways of xenobiotic metabolism in mammals
- appreciate the significance of metabolism in toxicology

- appreciate the major species differences in metabolism and their significance for toxicity testing
- understand the principles of toxicokinetics
- be able to integrate knowledge of kinetics, dynamics and metabolism in the study of toxicity
- understand the contribution of information on metabolism and toxicokinetics to the derivation of chemical specific adjustment factors

Module 3: Identification and assessment of genotoxic and non-genotoxic carcinogens

Module leaders:

Prof Emanuela Corsini, Department of Pharmacological Sciences, Faculty of Pharmacy, University of Milan and Prof Angelo Moretto, International Centre for Pesticides and Health Risk Prevention, University of Milan, Italy.

Content:

Chemicals, owing to a possible carcinogenic effect, are likely to endanger human health. This course module is designed to provide the participants with principles of genotoxicity and carcinogenesis and their application to risk assessment. A good knowledge of the principles of carcinogenesis is central to experimental toxicology and risk assessment. The information required for weighted risk assessment is provided by a systematic analysis of chemical and biological characteristics and thorough research into its mechanism of action. Topics covered will, therefore, include mechanisms of metabolic activation/deactivation of xenobiotics, interaction of xenobiotics with DNA, DNA repair, mechanisms of action, in vitro and in vivo assays, extrapolation of animal data to humans and novel models to assess carcinogenetic potential of chemicals. The main classes of genotoxic and carcinogenic agents and their mode of action will also be described. Central to this module will be the discussion of case studies aimed to provide the students with the tools necessary for a critical evaluation of animal data and their relevance to humans. In silico methods will also be discussed.

- Definition of genotoxic
- Test of mutagenicity
- Test of clastogenicity
- Evaluation and assessment of in vitro vs. in vivo tests (role of metabolism, dose issues)
- Epigenetics and its relevance in carcinogenicity
- Definition of carcinogen (genotox, non-genotox)
- Evaluation and assessment of in vivo carcinogenicity studies (statistics, background incidence, historical data, dose response, MTD, human relevance, IPCS framework, MOA, TTC)
- New methods: omics signature of carcinogens (in vitro/in vivo), transgenic models
- Use of (Q)SAR methods
- Case studies (phenobarbital/phenobarbital-like, dichlorvos, etc)

Learning outcomes:

- understand the fundamentals for risk assessment of genotoxic and non-genotoxic carcinogens and the human relevance of findings in experimental animals
- understand the role of xenobiotic-DNA interactions in cancer development
- appreciate the significance of in vitro vs. in vivo genotoxicity data
- appreciate the major species differences in mechanism/mode of action and their relevance for risk assessment
- be able to integrate knowledge of kinetics, dynamics and metabolism in the study of carcinogenicity
- be able to apply the framework of analysis of carcinogenic compounds
- understand the potential usefulness for risk assessment of new methods to study carcinogenicity, including "omics" and (Q)SAR methods

Module 4: Exposure analysis in risk assessment

Module leaders:

Dr Mieke Lumens and Prof Bas Blaauboer, Institute for Risk Assessment Sciences, Utrecht University, Netherlands

Content:

Exposure assessment and modelling are essential components of any risk assessment. The way in which exposure is assessed and modelled varies significantly and can range from generic qualitative assessments to highly quantitative approaches involving complex modelling. Exposure assessment requires an understanding of chemical, biological and physical principles and may involve estimating exposures from one to multiple sources of exposure.

In order to fully appreciate risks that arise from industrial activities and environmental emissions, it is essential to quantify chemical and biological agents that are emitted into general environment. In this course module, participants will learn to relate environmental conditions to actual exposures experienced by human populations and ecosystems. They will learn how to directly measure exposure levels, how to decide on the best way to obtain representative exposure measurements, and how to analyse data that is obtained during exposure measurement surveys.

Participants will also be introduced to fundamentals of exposure modelling, which allow investigators to infer exposure levels in absence of direct measurements of exposures. The growing amount of models aimed at estimating exposure with varying degrees of complexity leads to greater requirements for specialist expertise. Furthermore the recent move to towards developing genomic, proteomic and metabonomic methods to assess exposure adds further complexity to the field. These recent developments will be discussed during the course.

Learning outcomes:

- be acquainted with the principles of exposure assessment and its role in toxicology and risk assessment
- understand the importance and complexity of exposure assessment
- be able to critically evaluate different advanced exposure assessment methods
- be able to design strategies for exposure assessment

- be able to analyse and interpret exposure measurements applying different modelling tools (stochastic and deterministic)

Module 5: Identification and assessment of organ toxicity, including neurotoxicity, immunotoxicity

Module leaders:

Prof. Dr. Regine Kahl and Dr. Wim Wätjen, Institute of Toxicology, Heinrich Heine University of Düsseldorf, Germany

Content:

Identification of the target organ of toxicity is an important part of risk assessment. Organ toxicology is mainly assessed by animal experiments according to OECD guidelines although there is not yet a fixed international canon for the testing of neurotoxicity and immunotoxicity. The outcome of repeated dose studies is used for defining the no observed adverse effect level (NOAEL) or the benchmark dose, respectively, as the starting point of risk assessment. A key problem in the use of animal data is the relevance for humans with respect to the species differences in the mode of action and in metabolism, with respect to differences in the route and duration of administration, and with respect to sensitivity differences within the human population. Safety and uncertainty factors are at present used to account for such differences. Efforts are made all over the world to develop animal-free alternative methods for the assessment of organ toxicology.

- Assessment of organ toxicology by OECD guidelines for the testing of chemicals in single and repeated dose toxicity studies
- Histopathology of the liver, the kidney, the lungs, the hematopoietic system, the nervous system and the immune system in laboratory animals
- Methods for assessing immunotoxicology and chemical sensitisation
- The role of ADME in organ toxicology
- Modes of action (MOA) of toxic effects in laboratory animals as compared to humans: characterisation of the relevance of animal experiments to human health
- Organ toxicity as starting point for cancer development
- Dose response relationships in organ toxicology and definition of no observed adverse effect levels (NOAELs) and benchmark doses (BMDs)
- Extrapolation of data from laboratory animals to humans: characterisation of subpopulations sensitive to specific organ toxicities
- Extrapolation of data from laboratory animals to humans: definition of safety/uncertainty factors and route to route extrapolation
- Safety pharmacology in drug development
- Alternative testing strategies in organ toxicology

Learning outcomes:

- understand the histopathology and clinical signs of organ toxicity, including neurotoxicity and immunotoxicity
- be able to derive the relevant no observed adverse effect level (NOAEL) and/or benchmark dose (BMD) from a set of animal studies
- appreciate species differences in the mode of action (MOA) and metabolism and their significance for risk assessment

- be able to define safety/uncertainty factors for the extrapolation from animal experiments to exposure of human (sub)populations to chemicals,
- understand the state of the art of current efforts to reduce, refine and replace animal experiments by alternative testing methods

Module 6: Epidemiology and statistics in toxicological risk assessment

Module leaders:

Dr Mieke Lumens and Prof Bas Blaauboer, Institute for Risk Assessment Sciences, Utrecht University, Netherlands

Content:

Epidemiology can play an important role in risk assessment. Environmental epidemiology research can provide important information for risk assessment on a population level. The general objectives of this course are to increase the knowledge of principles and methods used in epidemiology. The focus will be on the use of epidemiology for risk assessment; on topics of interest to toxicologists such as genetic epidemiology, environmental and occupational epidemiology, and biomarkers in epidemiology; on basic data analysis in epidemiology; and on the relative merits of toxicology and epidemiology in the risk assessment process. While risks associated with environmental exposures are generally small the exposed population can be large. To detect these small risks it is essential that refined methods of epidemiology are used. Course participants will learn about measurement errors, bias and confounding. Next to the more traditional epidemiological designs like cohort or case control studies, more recently developed designs like time series designs, spatial methods and gene-environment interaction studies to describe mechanisms and susceptible populations will be discussed

Learning outcomes:

- understand the basic principles underlying epidemiologic research
- understand the epidemiological line of reasoning
- better understand epidemiological publications
- understand the strengths and weaknesses of epidemiological research
- understand the relative merits of toxicology and epidemiology in the risk assessment process
- understand the interface between toxicological and epidemiological studies

Module 7: Identification and assessment of reproductive toxicity and endocrine disruption

Module leaders:

Assoc prof Annika Hanberg, Prof Helen Håkansson, Institute of Environmental Medicine and Assoc prof Johanna Zilliacus, Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden

Content:

The course will include fundamental concepts in reproductive and developmental toxicity. Special attention will be paid to the endocrine toxicity mode-of-action. The course will cover complexities/difficulties in risk assessment and risk management including regulatory decision-making. Standardized test guidelines of reproductive

and endocrine disrupting effects will be covered. Specific attention will be given to the development of test strategies in OECD within the field. Attention will be paid to interpretation possibilities and evaluation of data from different test systems, handling of uncertainties and data gaps, and other problems in health risk assessment of reproductive toxicity and endocrine disruption. Particular focus will be given to identification of critical effects, extrapolation to humans and sensitive groups, application of assessment factors and allocation of health-based guidance values. Suggested limitations for EDCs in general risk assessment procedures will be discussed, e.g. shape of dose-response curve and epigenetic effects. Specific risk assessments of problematic chemicals will be discussed.

- Introduction to reproductive toxicity and endocrine disruption
- Introduction to endocrinology and nuclear receptor signalling
- Endocrine disruption – mechanisms, health effects, testing strategies
- Signalling pathways targeted by EDC
- Standardized test guidelines for reproductive toxicity, testing strategies for EDC
- Epidemiological studies of reproductive effects and endocrine disruption, interpretation of results
- Assessment of reproductive and EDC effect data (QSAR, *in vitro*, *in vivo*, epidemiology)
- Assessment of dose-response for endocrine effects
- Assessment of maternal toxicity
- Epigenetic effects of EDC, implications for risk assessment
- Regulatory aspects of reproductive toxicity and EDC - REACH, pesticides, CLP
- Examples of problematic risk assessment (e.g. Bisphenol A, Dioxin, vinclozolin)
- Group work on hazard and risk characterization

Learning outcomes:

- understand methods and procedures used in health risk assessment of reproductive toxicity and endocrine disrupters, as well as of the limitations involved
- be able to interpret toxicological and epidemiological studies of reproductive and endocrine toxicity for use in health risk assessment

Module 8: Supplementary module

Any other suitable course available in Europe on a specific aspect of risk assessment such as cosmetics, plant protection products and biocides, consumer products, medicines and veterinary drugs, contaminants in food, soil and water, industrial chemicals, occupational exposure, risk communication, 3Rs in risk assessment.

Applied training

The trainee obtains hands-on experience in performing toxicological risk assessments at an institution, authority or industry. The organisers can find a placement for the trainee or the applied training can be done in-house in the trainee's own institution/authority/company. The applied training should correspond to at least 450 hours. The applied training programme will take place from January 2011 to November 2011.

Monitoring of trainees and examination

Each trainee will have a mentor who will follow the progress of the trainee throughout the programme. During the applied training the trainee will also have a supervisor at the training institution. Each course module will have an examination and in addition there will be a final examination at the end of the programme. After the successful completion of the programme, the trainees will receive a certificate from the TRISK project describing the training.

Costs and financial support

There will be no fee for attending the training programme. However, in the case of a supplementary module that is provided by another institution the trainees will need to pay the appropriate course fee.

Trainees will have to cover their costs of travel and accommodation related to the participation to course modules and the applied training.

Trainees will receive a grant of 4000 € to contribute to the costs associated with attending the modules and the applied training. The grant money will be allocated as follows: 1000 € after the first module and 3000 € after passing the final examination. If the trainees terminate their course of study before the end of the programme they will be required to refund the money provided.

Additional financial support for trainees is offered by ILSI Europe and EUROTOX. ILSI Europe (<http://europe.ilsis.org>) offers one grant of up to 5.000 Euros (based on actual travel and accommodation costs) for a CEE, SEE and Baltic scientist (Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, The former Yugoslav Republic of Macedonia, Turkey).

EUROTOX (www.eurotox.com) offers two grants of 2.500 euro each to non-industry trainees. ILSI Europe and EUROTOX will select the grant receivers among the trainees who have been selected to participate in the TRISK training programme.

Eligibility criteria for the TRISK training programme are:

- 1a) Degree in toxicology (Master degree or similar degree) or
- 1b) Degree in another life science (such as medicine, veterinary medicine, biology, biochemistry, chemistry, environmental science, public health, bioengineering, food chemistry) and in addition, either (a) basic training in toxicology or (b) at least 2 years professional or research experience in toxicology/risk assessment (industry, national governments, consultancy companies, academia etc).
- 2) Citizenship or residence in a) EU member state, b) EFTA/EEA country, c) country to which the European Neighbourhood Policy applies, d) a country that is applying for, is candidate for, or is acceding to, membership of EU, e) the western Balkan countries.
- 3) Proficiency in the English language.

Selection

Trainees will be selected by a Selection Committee based on the selection criteria described below. A balance between nationalities of the participants will also be taken into account. Selection of at least 40% women will be aimed for. Twenty-five places are available.

Selection criteria	Assessment based on
Ability to successfully complete the training programme	Accomplished previous training, proficiency in English, letter of reference, letter of support from employer
Relevance of previous training and experience for the training programme	CV and description of previous experience
Impact and benefit of training to a future career in risk assessment	Motivation letter

Application procedure

Please complete the application form and also include

- 1) Brief CV that includes description of previous training including training in toxicology as well as description of proficiency in the English language
- 2) Short description of the applicant's previous work or research experience in toxicology/risk assessment (max 1 page)
- 3) A letter of motivation for participation in the training programme (max 1 page)
- 4) One letter of reference from a person who can provide a reference on the applicant's ability to successfully complete the programme
- 5) Description of possible funding for training programme from employer or other source
- 6) Letter of support from employer to ensure that the trainee will be able to participate in the training programme.

Deadline for application is October 16, 2009.

Send the application by e-mail to: Johanna Zilliacus, Karolinska Institutet, Sweden, E-mail: johanna.zilliacus@ki.se.

Reference letter and letter of support from employer can also be sent by fax (+46-8-711 66 59) or by post to Johanna Zilliacus, Karolinska Institutet, Dept of Biosciences and Nutrition, Division of Medical Nutrition, SE-141 86 Huddinge, Sweden.

Contact person: Johanna Zilliacus, Karolinska Institutet, Sweden, E-mail: johanna.zilliacus@ki.se, Tel. +46 8 6083329.

For further information and application form visit:
www.trisk-project.eu