20-21 NOVEMBER 2019

21ST ANNUAL CEFIC-LRI WORKSHOP

BRUSSELS, BELGIUM

LRI Long-Range Research Initiative | cefic

ADDRESSING MICROPLASTIC RISK ASSESSMENT: WHERE NEXT?

This is the topic of the thematic session of the 21ST edition of the Cefic-LRI Workshop. The rest of the event will mainly showcase presentations and posters from the most recent Cefic-LRI research projects covering key topics in human health (exposure modelling and assessment, in-vitro concentrations, carcinogen thresholds, etc.) and environmental (bioaccumulation, water solubility, adaptation of microbial communities, etc.) risk assessment.

Enjoy the experience!

2019 CEFIC-LRI AWARD CEREMONY

WEDNESDAY, 20 NOVEMBER 2019
BRUSSELS, STEIGENBERGER WILTCHER'S HOTEL

17.30 – 18.00	Registration
18.00 – 19.30	**Poster session & networking cocktail** *Illustrating recently started projects from 2019*
19.30 – 22.00	**CEFIC-LRI AWARD CEREMONY**

Cefic-LRI Award Ceremony Opening
Chair: Prof. Felix Carvalho, EUROTOX President Elect

Award 2018 project results: Quantitative evaluation of the Key Events Relationships resulting in impairment of learning and memory abilities to support regulatory decision-making
Dr David Pamies, Department of Physiology, Lausanne University, CH

2019 Cefic-LRI Innovative Science Award presentation
Dr Karolina Nowak, Division of Geobiotechnology, Institute for Biotechnology, Technical University of Berlin, DE

CEFIC-LRI AWARD CEREMONY

19.30 – 22.00

CHAIR

-

Prof. Felix Carvalho
President Elect
of EUROTOX

OPENING

Félix Carvalho, PharmD, PhD, ERT, is Full Professor of Toxicology at the Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto (FFUP) and a researcher at the Research Unit on Applied Molecular Biosciences (UCIBIO), Portugal.
Félix Carvalho is currently the President-Elect of EUROTOX (Association of European Toxicologists and European Societies of Toxicology); President of the Portuguese Society of Pharmacology; President of the Scientific Council of FFUP; Vice-Director of UCIBIO Research Unit; and a Member of the Medicines Evaluation Committee of the INFARMED National Authority of Medicines and Health Products.
Over the past 28 years, Félix Carvalho has published over 320 scientific articles/book chapters and is co-editor of two Books in the area of Toxicology.

2018 WINNER

-

Dr David Pamies
Department of
Physiology,
Lausanne University,
CH

PROJECT RESULTS

QUANTITATIVE EVALUATION OF THE KEY EVENTS RELATIONSHIPS RESULTING IN IMPAIRMENT OF LEARNING AND MEMORY ABILITIES TO SUPPORT REGULATORY DECISION-MAKING

David Pamies is a Postdoc at the Department of Physiology at Lausanne University. He got his master and PhD in Bioengineering at the Miguel Hernandez University. His motivation is to develop human in-vitro tools, which can be used within the regulatory and drug development context to understand and better classify the efficiency and toxicity of drugs. During his trainee period at the European Commission Joint Research Centre, he worked in new 3D models to assess developmental neurotoxicity (DNT). Afterwards, he joined the Centre for Alternatives to Animal Testing in January 2013, where he worked for five years on developing and application of an iPSC-derived 3D human brain model to study DNT and brain diseases. Now, he is working on the use of new in-vitro technologies to quantify adverse outcome pathways (AOPS) to help regulatory decision-making.

Regulatory toxicology faces three main problems: 1) thousands of chemicals lack toxicological information; 2) current test guidelines are expensive and very time consuming; and 3) most of the guidelines are based on animal experimentation. The NAS report on "Toxicity testing in the 21stcentury" highlighted the need for efficient and more human relevant in-vitro data. Recently in-vitro quantification of AOPs has been proposed as a possible solution to these problems. An AOP represents the existing knowledge concerning the causal links between the molecular initiating event and the cascade of key events (KE) that lead to a specific adverse outcome. Thanks to the funded grant by CEFIC-LRI we explored the possibility to quantified AOP13 by using a human 3D iPSC-derived model. In this presentation, the data obtained will be presented and discussed.

2019 WINNER

-

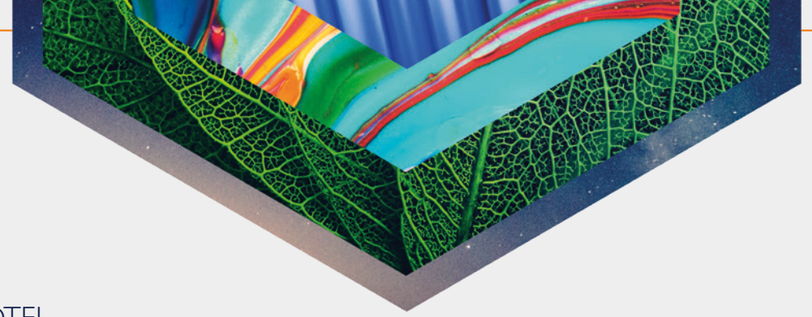
Dr Karolina Nowak,
Technische Universität
Berlin,
Division of
Geobiotechnology,
Institute for
Biotechnology

PROJECT PLANS

DEUTERIUM ISOTOPE PROBING (DIP) AS A NEW DIAGNOSTIC TOOL FOR THE ASSESSMENT OF BIODEGRADATION AND NON-EXTRACTABLE RESIDUES (NER) FORMATION IN REGULATORY TESTING OF ORGANIC CHEMICALS

Karolina Nowak received a Master Engineer Degree in Environmental Management from the University of Warmia and Mazury in Olsztyn, Poland in 2004; and a PhD in Environmental Chemistry from the RWTH Aachen University, Germany in 2011. She currently holds a postdoctoral position at Technische Universität Berlin (Division of Geobiotechnology). She is also a guest scientist at the Department of Environmental Biotechnology, Helmholtz-Centre for Environmental Research (UFZ). Karolina Nowak has ample experience in tracing the fate of chemicals in complex environments such as soils, sediments and plants using stable and radioactive tracers. She is a recipient of three awards for her approaches to identify biogenic non-extractable residues (bioNER) (German Chemical Society, Young Scientist at XV Symposium on Pesticide Chemistry, and International Symposium on Persistent Toxic Substances).

Prior to the final approval by ECHA, each chemical must be tested for its persistence and toxicity in numerous tests. Enhanced formation of non-extractable residues (NER) of unknown identity and low mineralisation may impede the approval. Proposed analytical methods and modelling approaches to characterise the NER in the recently published ECHA report are not satisfactory. Analytical methods are expensive and laborious whereas modelling approaches predicting the formation of NER do not yet correctly reflect the real and complex environmental conditions. The new approach - Deuterium Isotope Probing (DIP) - could be applied as a fast and cost-efficient tool for testing the biodegradation potential and the NER formation. In addition, the differentiation of the harmless biogenic NER from the potentially hazardous xenobiotic NER with DIP could be easier and avoid extensive biogenic NER analytics.



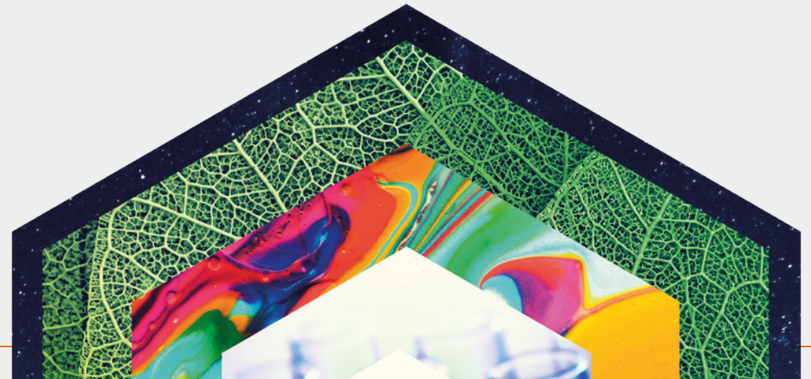
2019 CEFIC-LRI WORKSHOP

THURSDAY, 21 NOVEMBER 2019
BRUSSELS, STEIGENBERGER WILTCHER'S HOTEL

08.00 – 08.45	**Registration and welcome coffee**
08.45 – 09.00	**Word of welcome, programme overview** *Dr Heli Hollnagel, Dow, CH/Cefic LRI Issue Team Chair*
09.00 – 10.00	**THEMATIC SESSION: ADDRESSING MICROPLASTIC RISK ASSESSMENT: WHERE NEXT?** *Chair: Dr Jens Otte, BASF, DE*
09.00 – 09.20	**Towards the development and application of an environmental risk assessment framework for microplastic particles** *Dr Todd Gouin, EnvironResearch, UK*
09.20 – 09.40	**Microplastics and health: particles past, present and future** *Dr Stephanie Wright, UKRI Rutherford Fellow, MRC Centre for Environment and Health, King's College London, UK*
09.40 – 10.00	**Speakers discussion: questions from the audience**
10.00 – 13.00	**PLENARY SESSION I: HUMAN HEALTH RISK ASSESSMENT** Finishing LRI projects with impact on exposure modelling and assessment, in-vitro concentrations, and carcinogen thresholds *Chair: Dr Bruno Hubesch, LRI Programme Consultant, Innovation, Cefic, BE*
10.00 – 10.30	**AIMT7 - RVis: Open Access PBPK Modelling Platform** *Dr George Loizou, Health and Safety Laboratory, Buxton, UK*
10.30 – 11.00	**ECO36 - Paving the way for QIVIVE – from nominal to free to cellular concentrations in in vitro assay** *Prof. Beate Escher, Helmholtz Centre for Environmental Research, Leipzig, DE*
11.00 – 11.30	**Coffee break**
11.30 – 12.00	**B17 - SHINE: Target and non-target Screening of cHemicals in the Indoor enviroNment for human Exposure assessment** *Dr Marja Lamoree, Vrije Universiteit Amsterdam, NL*
12.00 – 12.30	**B18.2 - Incorporation of repeated dose study information for non-DNA-reactive carcinogens into the CPDB database and analysis of threshold values** *Dr Monika Batke, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, DE*
12.30 – 13.00	**B20 - Experimental assessment of inhalation and dermal exposure to chemicals during industrial and professional activities** *Dr Wouter Fransman, Netherlands Organisation for Applied Scientific Research (TNO), Zeist, NL*
13.00 – 14.30	**Lunch**
14.30 – 16.30	**PLENARY SESSION II: ENVIRONMENTAL RISK ASSESSMENT** Finishing LRI projects with impact on bioaccumulation, water solubility and adaptation of microbial communities *Chair: Dr Bruno Hubesch, LRI Programme Consultant, Innovation, Cefic, BE*
14.30 – 15.00	**ECO29 - CHEMADAPT - Application of chemostat systems to include adaptation of microbial communities in persistency testing** *Prof. John Parsons, University of Amsterdam, NL*
15.00 – 15.30	**ECO34 - A tiered testing strategy for rapid estimation of bioaccumulation by a combined modelling – in vitro testing approach** *Prof. Kristin Schirmer, Swiss Federal Institute of Aquatic Science and Technology, Dübendorf, CH*
15.30 – 16.00	**ECO37 - D-BASS – Developing a Bioaccumulation Assessment Strategy for Surfactants** *Prof. Steven Droge, University of Amsterdam, NL*
16.00 – 16.30	**ECO38 - Cross-validation for improving determinations of water solubility for difficult to test substances** *Prof. Philipp Mayer, Technical University of Denmark, Lyngby, DK*
16.30 – 16.40	**Cocktails in Stresa** *Dr Rick Becker, American Chemistry Council (ACC), US*
16.40 – 16.50	**Conclusions of the workshop and future perspectives on the Cefic-LRI programme** *Dr Pierre Barthelemy, Executive Director, Innovation, Cefic, BE*
16.50 – 17.00	**Close of Cefic-LRI Workshop 2019** *Dr Bruno Hubesch, LRI Programme Consultant, Innovation, Cefic, BE*
17.00	**Networking Coffee**

POSTERS

AIMT5.2 A COMPUTATIONAL MODEL FOR NEURAL TUBE CLOSURE FOR IN SILICO PREDICTIVE TOXICOLOGY OF NEURAL TUBE DEFECTS	Prof. Dr Aldert Piersma *RIVM* *Bilthoven, NL*
B12.3 EXTENSION AND EXPERIMENTAL VALIDATION OF THE MULTI-PATHWAY EXPOSURE MODEL DUSTEX	Prof. John Little *Virginia Tech (VT)* *Blacksburg, VA, USA*
B15.3 ECEL V3.0: TECHNICAL IMPROVEMENTS AND POPULATION OF THE INTEGRATED RISK MANAGEMENT MEASURE (RMM) LIBRARY	Dr Wouter Fransman *TNO* *Zeist, NL*
B19.2 REFINEMENT OF A FRAMEWORK FOR EXTRAPOLATING OF WORKER EXPOSURE MEASUREMENT DATA	Dr Wouter Fransman *TNO* *Zeist, NL*
B21 IN VITRO DATA TO PARAMETERISE PBPK MODELS FOR INHALATION EXPOSURE	Dr Katharina Schwarz *Fraunhofer ITEM* *Hannover, DE*
C7 ELUMICA: ELUCIDATING MICROBIAL METABOLIC CAPACITY	Dr Saskia Sperber *BASF SE* *Ludwigshafen, DE*
ECO40.2 INVESTIGATIONS ON THE BIOCONCENTRATIONS OF XENOBIOTICS IN THE FRESHWATER AMPHIPOD HYALELLA AZTECA AND INTER-LABORATORY COMPARISON OF A NEW BCF TEST PROTOCOL	Prof. Dr Christian Schlechtriem *Fraunhofer IME* *Schmallenberg, DE*
ECO47 SNAPFISH: SEARCHING FOR REFINED IN VITRO APPROACHES TO PREDICT BIOCONCENTRATION IN FISH	Dr Kilian Smith *RWTH Aachen University* *Aachen, DE*
ECO48 NANO2PLAST: EXTENDING NANOPARTICLE MODELS TO OPEN SOURCE MODELS OF THE FATE AND TRANSPORT OF MICROPLASTIC IN AQUATIC SYSTEMS	Prof. Matthew MacLeod *Stockholm University* *Stockholm, SE*
ECO49 METAS: MICROPLASTIC EFFECT THRESHOLDS FOR AQUATIC SPECIES	Prof. Bart Koelmans & Vera de Ruijter *Wageningen University* *Wageningen, NL*
ECO50 GETREAL: INCORPORATING SPATIAL AND SEASONAL VARIABILITY IN COMMUNITY SENSITIVITY INTO CHEMICAL RISK ASSESSMENT	Prof. Dr Ralf B. Schäfer *University of Koblenz-Landau* *Landau, DE*
EMSG59 DEVELOPING A QUANTITATIVE AOP FOR LIVER-MEDIATED THYROID MODULATION AFTER PRENATAL EXPOSURE TO A XENOBIOTIC COMPOUND IN THE RAT	Prof. Dr Aldert Piersma *RIVM* *Bilthoven, NL*



Dr Heli Hollnagel
Dow Europe,
CH/Cefic-LRI Issue
Team Chair

WORD OF WELCOME

PROGRAMME OVERVIEW

08.45 – 09.00

CHAIR
-
Dr Jens Otte
Regulatory
Ecotoxicology
Chemicals,
BASF SEBASF, DE

THEMATIC SESSION

ADDRESSING MICROPLASTIC RISK ASSESSMENT: WHERE NEXT?

09.00 – 10.00

Over the past years, microplastics and plastics in the environment have seen increasing attention in the scientific community but also in media coverage. Following this, the topic has also found broad attention in the public and for policy makers.

With this thematic session, we want to keep the focus on approaches in environmental sciences and human health for addressing microplastics risk assessment. As this is a fast-moving scientific area, here we present current state-of-the-art knowledge about microplastics and highlight some insights and complexities of the topic. Conventionally, this topic has been approached separately within individual disciplines, however present developments indicate that the issue merits a multidisciplinary approach to identify common goals for focused microplastics risk assessment in the future.

Dr Todd Gouin
EnvironResearch, UK

TOWARDS THE DEVELOPMENT AND APPLICATION OF AN ENVIRONMENTAL RISK ASSESSMENT FRAMEWORK FOR MICROPLASTIC PARTICLES

Plastic waste emissions to the environment and subsequent degradation into microplastic particles (MPs) represents a global concern given their potential to interact with biota. Current understanding of the potential impacts from MPs on aquatic and terrestrial population stability and ecosystem structure and function, however, is insufficient to fully assess these environmental risks. This presentation will summarise the conclusions of an International Council of Chemical Associations (ICCA) sponsored symposium where participants were asked to consider the following: Discuss the scientific merits and limitations of 1) applying a proposed conceptual environmental risk assessment (ERA) framework for MPs and 2) identify and prioritise major research needs in applying ERA tools for MPs.

Dr Stephanie Wright
UKRI Rutherford Fellow,
MRC Centre
for Environment
and Health,
King's College London,
UK

MICROPLASTICS AND HEALTH: PARTICLES PAST, PRESENT AND FUTURE

Microplastics are a complex class of heavily modified, synthetic organic particulates which contaminate a range of environments. Laboratory studies indicate that at high exposure concentrations they can negatively impact biota, primarily via oxidative stress and metabolic disruption. Recently, the presence of microplastics in water, food and the air we breathe has raised concern for public health due to the potential for exposure via diet and inhalation, although the health impacts this has are largely unknown. The risk for harm is dependent on dose, which is influenced by exposure concentration and in vivo particle kinetics and biodistribution. The parameters which may contribute to toxicity include size, durability, and dimension, which vary greatly depending on the microplastic type. This talk will draw on past and current literature across occupational health to particle toxicology, to present an overview on the existing evidence for microplastics to cause harm. It will present some case scenarios and discussion on whether we should be concerned of a 'plastic' effect and highlight where the field needs to progress.

PLENARY SESSION I

HUMAN HEALTH RISK ASSESSMENT

FINISHING LRI PROJECTS WITH IMPACT ON EXPOSURE MODELLING AND ASSESSMENT, IN-VITRO CONCENTRATIONS, AND CARCINOGEN THRESHOLDS

10.00 – 13.00

CHAIR

-

Dr Bruno Hubesch
LRI Programme Consultant, Innovation, Cefic, BE

PROJECT PRESENTATION

AIMT7 - RVIS

AN OPEN ACCESS PBPK MODELLING PLATFORM

10.00 – 10.30

Dr George Loizou
Health and Safety Laboratory, Buxton, UK

The widespread adoption and application of PBPK modelling in chemical product development and safety assessment has been hampered by criticism that these models are data hungry, resource intensive, complex and require high levels of mathematical expertise and programming skills. A software tool that can reduce reliance on these specialist skills, whilst not eliminating them, should facilitate increased use of PBPK modelling. In addition, a software tool that can shift the emphasis to understanding the biology of toxicity and disease, which underpins chemical safety and risk assessment, should also help address these problems. However, the greatest obstacle to the more widespread adoption of PBPK modelling is most likely the availability of a common, transparent and independently auditable, free-to-use platform for running models and analysing model structure and output. In response to this need, a prototype version of such a tool called, R-Vis, a general-purpose modelling platform for models written in the free, open source syntax R, was developed initially with support from the European Partnership for Alternative Approaches to Animal testing (EPAA). The further development of R-Vis was supported by Cefic-LRI to provide a more robust and intuitive, user-friendly platform for PBPK model development, model structure analysis and application that include aspects of an emerging Good Modelling Practice (GMP) for PBPK. The realistic, although simplified descriptions of biology captured in PBPK models requires an approach to the evaluation of model structure and parameter uncertainty that can account for the non-linear behaviour of some biological processes e.g., saturation of enzyme activity. Therefore, R-Vis deploys global as opposed to local sensitivity analysis, which is an important component of GMP. Another important feature of this tool is a discrete module for Parameter Estimation used for the prediction of equivalent oral, dermal or inhalation exposures that are consistent with human biological monitoring data. This type of reverse dosimetry prediction is best achieved using a probabilistic PBPK model to incorporate human inter-individual variability in pharmacokinetics and incorporating a rigorous Bayesian statistical framework for accommodating uncertainty in both the parameters of a PBPK model and lack of fit of the model to measured data. Finally, the structure of the R-Vis platform allows the future addition of modules, for example, an intuitive user interface for an in vitro concentration–response to in-vivo dose-response translation which would contribute to the 3Rs (Reduction, Refinement, Replacement) of animals in toxicological testing.

PROJECT PRESENTATION

ECO36

PAVING THE WAY FOR QIVIVE – FROM NOMINAL TO FREE TO CELLULAR CONCENTRATIONS IN IN-VITRO ASSAY

10.30 – 11.00

Prof. Beate Escher
Helmholtz Centre for Environmental Research, Leipzig, DE

We developed experimental approaches and models to derive dose-metrics amenable for in-vitro to in-vivo extrapolation (QIVIVE), such as freely dissolved and cellular effect concentrations. High volatile losses and crossover were seen for semi-volatile and hydrophobic test chemicals in in-vitro assays. Due to its high sorptive capacity, the medium served as a passive dosing device but also decreased the bioavailability. The time-resolved freely dissolved concentrations in in-vitro bioassays in 96-well plate format were measured for a suite of neutral and ionic organic chemicals with solid-phase microextraction. The experimental effect concentrations were used to validate a mass balance/partition model that can predict the freely dissolved and cellular effect concentrations for any well-plate format, medium and cells, provided that the lipid- and protein content of the medium and cells are known. Kinetic resolution of the model was provided for 2D reporter gene assays and more complex 3D cell models were explored for use in repeat-dose techniques.

PROJECT PRESENTATION

B17

SHINE: TARGET AND NON-TARGET SCREENING OF CHEMICALS IN THE INDOOR ENVIRONMENT FOR HUMAN EXPOSURE ASSESSMENT

11.30 – 12.00

Dr Marja Lamoree
Vrije Universiteit Amsterdam, NL

When indoors, people are exposed to a broad range of compounds from a variety of compound classes. Indoor dust is a sink for chemicals and may be a source of exposure to chemicals for humans in every life stage. Target and non-target screening of chemicals in the indoor environment for human exposure assessment was carried out in the SHINE project (LRI-B17) focusing on dust and air samples from homes, offices and daycare centres in several European countries. Target analysis included novel brominated flame retardants, HBCDDs, organophosphate flame retardants, per and polyfluorinated alkyl substances, chlorinated paraffins, plasticisers and pesticides. With the RAIDAR-ICE model (Risk Assessment, Identification and Ranking – Indoor & Consumer Exposure), modelling of human exposure to chemicals from near-field sources was carried out.

Dr Monika Batke
Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, DE

PROJECT PRESENTATION

B18.2

INCORPORATION OF REPEATED DOSE STUDY INFORMATION FOR NON-DNA-REACTIVE CARCINOGENS INTO THE CPDB DATABASE AND ANALYSIS OF THRESHOLD VALUES

12.00 – 12.30

This project is the extension of the CEFIC-LRI project "Database on Carcinogen Dose-response, including Information on DNA-reactivity, for TTC and beyond".
This previous project updated the CPDB database by including more recent studies, labelling genotoxic and non-genotoxic carcinogens and adding TD50/TD25/TD10 and BMDL10 values from the dose response of the tumor finding.
The current project updated the CPDB database by adding non-neoplastic or pre-neoplastic lesions and their corresponding NOELs for the non-DNA-reactive substances to derive threshold-based health-based guidance values. The resulting TTC values for non-DNA-reactive substances are presented and discussed. This closes the gap in evidence supporting the approach of applying the non-cancer Cramer Class thresholds to substances without concern for DNA-reactivity.

Dr Wouter Fransman
Netherlands Organisation for Applied Scientific Research (TNO), Zeist, NL

PROJECT PRESENTATION

B20

EXPERIMENTAL ASSESSMENT OF INHALATION AND DERMAL EXPOSURE TO CHEMICALS DURING INDUSTRIAL AND PROFESSIONAL ACTIVITIES

12.30 – 13.00

The development of exposure models is hampered by scarcity of exposure data as well as by lack of information on relevant exposure factors and conditions of exposure. For that reason, new inhalation and dermal exposure data measured during simulated work activities performed under a controlled experimental setting have been collected. Measurement results were compared against worker exposure estimates provided by the ECETOC TRA model to assess where the model could be improved. Five activities (PROCs 4, 5, 10, 13, 19) were selected for this study and resulted in 70 quantitative hand measurements, 32 quantitative inhalation measurements and 70 photographs taken under UV light. This study gave good insights into dermal as well as inhalation exposure levels during selected worker tasks (PROCs) in comparison to ECETOC TRA model estimates.

CHAIR
-
Dr Bruno Hubesch
LRI Programme Consultant, Innovation, Cefic, BE

PLENARY SESSION II

ENVIRONMENTAL RISK ASSESSMENT

FINISHING LRI PROJECTS WITH IMPACT ON BIOACCUMULATION, WATER SOLUBILITY AND ADAPTATION OF MICROBIAL COMMUNITIES

14.30 – 16.30

Prof. John Parsons
University of Amsterdam, NL

PROJECT PRESENTATION

ECO29

CHEMADAPT – APPLICATION OF CHEMOSTAT SYSTEMS TO INCLUDE ADAPTATION OF MICROBIAL COMMUNITIES IN PERSISTENCY TESTING

14.30 – 15.00

Chemostat systems were used to study the impact of long-term exposure to N-methylpiperazine (NMP), 4-chloroaniline (4CA) and metformin (MET) of activated sludge microbial communities on enhanced biodegradation tests following the OECD 310 guideline. After one month of exposure, the community exposed to NMP was adapted and could completely degrade it within 10 days in the RBTs, but the communities exposed for months to 4CA and MET lost part of their ability to degrade these compounds. Long-term exposure of five activated sludge samples to these chemicals did result in lower variability of the test results despite the inocula composition being significantly different, but this may be partially affected by the test volume and the inoculum quantity. Although this project may contribute to the development of enhanced testing protocols, we do not recommend using chemostat systems to prepare inocula for regulatory ready biodegradability testing.

Prof. Kristin Schirmer
Swiss Federal Institute of Aquatic Science and Technology, Dübendorf, CH

PROJECT PRESENTATION

ECO34

A TIERED TESTING STRATEGY FOR RAPID ESTIMATION OF BIOACCUMULATION BY A COMBINED MODELLING – IN-VITRO TESTING APPROACH

15.00 – 15.30

This research funded under the umbrella of CEFIC-LRI/Eco34 seeks to improve alternative methods to estimate bioaccumulation of organic chemicals in fish. We follow a tiered strategy that integrates toxicokinetic (TK) models, quantitative structure-activity relationships (QSARs), in-vitro experimental data from fish liver, gill, and intestinal tissues, and in-vitro to in-vivo extrapolation methods. In a first step, we derived a list of candidate chemicals for in-vitro testing based on model discrepancies, availability of reliable in-vivo BCF and BMF data, and availability of in-vitro biotransformation rates. The resulting chemicals were divided into three Kow categories based on predominant exposure route(s) to guide in-vitro testing: 1) log Kow <4 (aqueous exposure dominates – to be tested in gill and liver models); 2) log Kow 4 - 5.5 (mixed exposure routes – to be tested in gill, liver and intestine models); and 3) log Kow>5.5 (dietary exposure dominates – to be tested in liver and intestinal models). In the second step, rainbow trout (Oncorhynchus mykiss) derived in-vitro models, representing the gill, liver and intestine, were used to derive in-vitro biotransformation rate constants, monitoring the loss of parent compound in each in-vitro system over time. Specifically, primary gill cell cultures grown on permeable supports were used to determine the combined biotransformation/permeation rate through this epithelial model. S9 preparations from hepatocytes and intestine yielded biotransformation rate constants following the protocol outlined in the OECD guideline 319. Permanent cell lines of gills (RTgill-W1), liver (RTL-W1) and intestine (RTgutGC), exposed in monolayer, complemented the set of in-vitro methods applied. In-vitro models were each applied under their respective optimal conditions taking, for example, temperature and media composition into account. Chemical starting concentrations were set uniformly for all models as far as possible, based on non-toxic concentrations and analytical method sensitivity.

It can be stated overall that the derivatives of all three tissues contributed to the biotransformation of the chemicals. Yet, both the liver and intestine-derived models yielded higher rates of biotransformation than the gill in-vitro systems. Apart from a few exceptions, the respective CL_invitro were comparable across the different in-vitro systems; this was also true with respect to indicating whether a chemical was biotransformed at all or not. The details of the experimental data will be presented in the poster.

Prof. Steven Droge
University of Amsterdam, NL

PROJECT PRESENTATION

ECO37

D-BASS – DEVELOPING A BIOACCUMULATION ASSESSMENT STRATEGY FOR SURFACTANTS

15.30 – 16.00

The ECO37 project aimed to improve the bioconcentration factor (BCF) predictions for surfactants. Surfactants are challenging chemicals to assess by modelling efforts. Surfactants are often ionised organic chemicals while existing models are optimised to deal with neutral chemicals. Also, very little partitioning data is available because surfactants often emulsify solvents (e.g. octanol into water) and sorb onto all kinds of interfaces during experimental studies, hampering adaptation of models to include surfactants. Starting points of this study were the availability of a BCF model which addressed ionisable chemicals (BIONIC), the availability of artificial cell membranes as ideal sorbents, an OECD protocol for in-vitro hepatic clearance (S9), and a lack of adequate fish BCF data for many surfactant types to rigorously evaluate model performance. ECO37 addressed three key parts to progress surfactant assessment. Toronto based consultants from ARC and AES focused on optimising study designs and modelling improvements, University of Amsterdam collected key in-vitro parameters, and Stockholm University determined consistent reference in-vivo fish BCF values. With the project nearly finished, we can now integrate the in-vitro parameters as key input values in the adapted BIONIC model, to compare with new experimental in-vivo BCF data. Integrated evaluation is becoming available for a wide range of cationic surfactants as key examples, focusing on chain length, ionisation state, pH effects, tissue distribution and metabolite formation.

Prof. Philipp Mayer
Technical University of Denmark, Lyngby, DK

PROJECT PRESENTATION

ECO38

CROSS-VALIDATION FOR IMPROVING DETERMINATIONS OF WATER SOLUBILITY FOR DIFFICULT TO TEST SUBSTANCES

16.00 – 16.30

Water solubility is one of the most frequently used physical-chemical properties of chemicals. The OECD guideline for measuring solubility dates back to 1995 and is limited to mono-constituent, stable and non-volatile substances. The aims of this project were to: (1) review the literature and give tutorial guidance about solubility measurements of difficult to test chemicals; (2) conduct a small ring test for hydrophobic chemicals using slow-stirring and column elution methods; and (3) develop, apply and test passive dosing for determining water solubility of liquid hydrophobic chemicals. Methods to handle highly hydrophobic chemicals and volatile chemicals, and methods to rapidly saturate water with fast degrading chemicals were reviewed. A decision tree will be presented outlining the preferred choice of method for each chemical group.

Dr Rick Becker
American Chemistry Council (ACC), US

COCKTAILS IN STRESA

16.30 – 16.40

Dr Pierre Barthelemy
Executive Director, Innovation, Cefic, BE

CONCLUSIONS OF THE WORKSHOP AND FUTURE PERSPECTIVES ON THE CEFIC-LRI PROGRAMME

16.40 – 16.50

Cefic-LRI Programme

European Chemical Industry Council - Cefic aisbl

CHEMISTRY MAKING A WORLD OF DIFFERENCE

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European Chemical Industry Council
Rue Belliard 40 (box 15)
B - 1040, Brussels
Tel: + 32 2 436 9415
mail@cefic.be
www.cefic.org

Long-Range Research Initiative

LRI SECRETARIAT

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Tel: +32 2 436 9415
lri@cefic.be
www.cefic-lri.org