ADDRESSING MICROPLASTIC RISK ASSESSMENT: WHERE NEXT?

This is the topic of the thematic session of the 21\textsuperscript{st} 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 WILTCHEER’S HOTEL

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<td>17.30 – 18.00</td>
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<td>18.00 – 19.30</td>
<td>Poster session &amp; networking cocktail</td>
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<td>19.30 – 22.00</td>
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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 GeneticEngineering, Institute for Biotechnology, Technical University of Berlin, DE
DECISION-MAKING
IMPAIRMENT OF LEARNING AND MEMORY ABILITIES TO SUPPORT REGULATORY
QUANTITATIVE EVALUATION OF THE KEY EVENTS RELATIONSHIPS RESULTING IN
PROJECT RESULTS

Quantitative Evaluation of the Key Events Relationships Resulting in Impairment of Learning and Memory Abilities to Support Regulatory Decision-Making

David Parnies is a Postdoc at the Department of Physiology at Lausanne University. He got his master and PhD in Biogenesis 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 in 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 new 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 21st century” 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 AOP13 by using a human 3D iPSC-derived model, Félix Carvalho has published over 320 scientific articles/book chapters and is co-author of two books in the area of Toxicology.

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 Masury 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 (Jülich). 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 mineralization 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 predict the formation of NER do not yet correctly reflect the real and complex environmental conditions. The new approach - Deuteration isotope Probing (DIP) - could be applied as a fast and cost-efficient tool for seeing the bioavailability 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 biogeochemical modelling analyses.
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. Hel Hahnaget, Dow, CEFIC-LRI Issue Team Chair

09.00 – 10.00 THEMATIC SESSION: ADDRESSING MICROPOLYSTERIC RISK ASSESSMENT: WHERE NEXT? Chair: Dr Jens Otto, 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, NERC Centre for Environmental and Health, King’s College London, UK

09.40 – 10.00 Speakers discussion: questions from the audience

10.00 – 11.30 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, ULI 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. Manika Baske, 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. Manuela Rehman, Netherlands Organisation for Applied Scientific Research (TNO), Zeele, 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, ULI 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 – 17.00 Close of Cefic-LRI Workshop 2019
Dr. Bruno Hubesch, ULI Programme Consultant, Innovation, Cefic, BE

17.00 Networking Coffee
POSTERS

AIMTS 32
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
ECOL v3.0: TECHNICAL IMPROVEMENTS AND POPULATION OF THE INTEGRATED RISK MANAGEMENT MEASURE (IRM) LIBRARY

Dr-Wouter Fransman
TNO
Zeist, NL

B19.2
REFINEMENT OF A FRAMEWORK FOR EXTRAPOLATING OF WORKER EXPOSURE MEASUREMENT DATA

Dr Katharina Schwarz
Fraunhofer ITEM
Hanover, DE

B21
IN VITRO DATA TO PARAMETERISE PBPK MODELS FOR INHALATION EXPOSURE

Dr Saskia Sperber
BASF SE
Ludwigshafen, DE

C7
ELUMICA: ELUCIDATING MICROBIAL METABOLIC CAPACITY

Dr. Christian Schlechtriem
Fraunhofer IME
Schmuckenberg, 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

Dr. Kilian Smith
RWTH Aachen University
Aachen, DE

ECO47
SNAPFISH: SEARCHING FOR REFINED IN VITRO APPROACHES TO PREDICT BIOCONCENTRATION IN FISH

Dr. Matthew MacLeod
Stockholm University
Stockholm, SE

ECO48
NANO2PLAST: EXTENDING NANOPARTICLE MODELS TO OPEN SOURCE MODELS OF THE RATE AND TRANSPORT OF MICROPLASTIC IN AQUATIC SYSTEMS

Prof. Bart Keoleman & Vera de Ruijter
Wageningen University
Wageningen, NL

ECO49
METAS: MICROPLASTIC EFFECT THRESHOLDS FOR AQUATIC SPECIES

Prof. Dr Ralf B. Schäfer
University of Koblenz-Landau
Landau, DE

ECO50
GETREAL: INCORPORATING SPATIAL AND SEASONAL VARIABILITY IN COMMUNITY SENSITIVITY INTO CHEMICAL RISK ASSESSMENT

Prof. Dr Aldert Piersma
RIVM
Bilthoven, NL

EMSG59
DEVELOPING A QUANTITATIVE AOP FOR LIVER-MEDIATED THYROID MODULATION AFTER PRENATAL EXPOSURE TO A XENOBIOTIC COMPOUND IN THE RAT

Prof. John Little
Virginia Tech (VT)
Blacksburg, VA, USA

Prof. Dr Ralf B. Schäfer
University of Koblenz-Landau
Landau, DE
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.

THEMATIC SESSION

ADDRESSING MICROPLASTIC RISK ASSESSMENT: WHERE NEXT?

09.00 – 10.00

Dr Jens Otte
Regulatory Ecotoxicology
Chemicals,
BASF SE

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 Todd Gouin
EnvironResearch, UK

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

09.00 – 10.00

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

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.

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

MICROPLASTICS AND HEALTH: PARTICLES PAST, PRESENT AND FUTURE

09.00 – 10.00

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

WORD OF WELCOME

PROGRAMME OVERVIEW

08.45 – 09.00

Dr Jens Otte
Regulatory Ecotoxicology
Chemicals,
BASF SE

09.00 – 10.00

Dr Todd Gouin
EnvironResearch, UK

09.00 – 10.00

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

09.00 – 10.00

Dr Heli Hollnagel
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CH/CEFIC-LRI Issue Team Chair

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Regulatory Ecotoxicology
Chemicals,
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EnvironResearch, UK

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

09.00 – 10.00

Dr Heli Hollnagel
Dow Europe,
CH/CEFIC-LRI Issue Team Chair
AN OPEN ACCESS PBPK MODELLING PLATFORM

10.00 – 10.30

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, while 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 comprehensive, transparent and independently auditable, free-to-use platform for running models and analysing model output.

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 surge capacity, the medium served as a passive dosing device but also decreased the bioavailability. The time-resolved freely dissolved concentrations in in-vitro biosays 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.

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 (LAB-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, par 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.
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/TD50/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 Monika Batke
Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, DE

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 (PROC 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 (PROC(s)) in comparison to ECETOC TRA model estimates.

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

PLENARY SESSION II

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

14.30 – 16.30

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. 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. John Parsons
University of Amsterdam, NL
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 routes: aqueous exposure to test chemicals; (2) conduct a small ring test for volatile substances; and (3) 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 co-solvent techniques; and (3) conduct a ring test for surfactants. The project was 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 metabolism.
COCKTAILS IN STRESA
16.30 – 16.40

CONCLUSIONS OF THE WORKSHOP AND FUTURE PERSPECTIVES ON THE CEFIC-LRI PROGRAMME
16.40 – 16.50