Title: The Application of Emerging Tools for Bioaccumulation Assessment: Integration of Biotransformation

Date: Sunday May 13, 2018 (08:00 – 17:00)

Location: Hotel dei Congressi, Viale Shakespeare, 29 – 00144 Roma (To Be Confirmed)

Abstract: Thousands of chemicals are being screened for their Persistence, Bioaccumulation and Toxicity (PBT), and various lines of evidence (LOEs) are available to assess bioaccumulation. In vivo laboratory-based lines of evidence include the bioconcentration factor (BCF) and biomagnification factor (BMF). In vitro biotransformation rate data (S9, hepatocytes) can also be applied for bioaccumulation assessment using in vitro- in vivo extrapolation (IVIVE) methods. Field-based LOEs include the BMF, bioaccumulation factor (BAF), and the Trophic Magnification Factor (TMF). In silico LOEs include quantitative structure-activity relationships (QSARs) for the BCF and the biotransformation rate constant (k_B) and mass balance bioaccumulation (toxicokinetic) models. The Bioaccumulation Assessment Tool (BAT) integrates relevant measured and modelled data in a user-friendly, organizational framework and computational tool to provide a weight of evidence (WOE) approach for B assessment. This course will overview some new methodologies and approaches to incorporate estimates of biotransformation (in vitro fish biotransformation assays and QSAR model predictions), and provide instruction on how these and other LOEs for bioaccumulation assessment can be integrated into the BAT.

This course is an advanced course, aimed at registrants and evaluators familiar with bioaccumulation assessment and chemical evaluation / assessment.

Objectives:

- Provide an overview of the newly-developed rainbow trout liver S9 fraction and cryopreserved trout hepatocyte substrate depletion assays for the evaluation of xenobiotic biotransformation in fish
- Highlight and discuss recent advances for in silico predictions of biotransformation
- Provide an introduction and overview of the Bioaccumulation Assessment Tool (BAT)
- Demonstrate the application of BAT using illustrative hands-on case examples

Products/Course materials:

- Course book (to be prepared by instructors) containing:
    - BAT User Guide
    - Draft OECD Test Guidelines and Guidance Document
    - Other relevant materials
- Access to BAT (VBA/Excel)

Attendance Requirements:

- Pre-registration
- Bring wireless-enabled laptops with USB

Draft Training Course Outline:

8:00 Introductions & course overview *(Michelle Embry, HESI; Jon Arnot, ARC)*

Part I: Fish in vitro biotransformation method (~2 hours)

8:15 Introduction of in vitro methods *(Michelle Embry, HESI)*

8:25 Review of methods – S9 & Hepatocytes (e.g., draft OECD TGs) *(Karla Johanning, KJ Scientific and KJ Scientific GmbH)*

9:10 Application of the methods & caveats (e.g., discussion of parts from OECD GD) *(Heike Laue, Givaudan)*

9:45 Coffee Break

10:00 In vitro-in vivo extrapolation models for biotransformation rates *(Jon Arnot, ARC)*

Part II: QSAR (~1 hour)

10:15 Introduction to QSARs (*Ester Papa, U of Insubria)*

10:45 Biotransformation QSARs & software demonstration *(Alessandro Sangion, U of Insubria)*

Part III: BAT (~4.5 hours)

11:15 Introduction to BAT *(Jon Arnot, ARC)*

11:30 BAT part I *(Liisa Toose, ARC)*

12:00 – 13:00 Lunch

13:00 BAT part II *(James Armitage, AES)*

14:00 Hands-on BAT: worked/presented case examples (*Jon Arnot, ARC*)

14:45 Coffee break

15:00 Hands-on IVIVE and BAT (*All*)

16:45 – 17:00 Course evaluation

17:00 Adjourn

Course Instructors *(please see Annex 1 for short instructor bios, relevant experience):*

Jon Arnot, PhD (ARC) ***[co-lead]***
President, ARC Arnot Research & Consulting
36 Sproat Avenue, Toronto, ON, Canada, M4M 1W4
1-647-225-3771
jon@arnotresearch.com

Michelle Embry, PhD (HESI) ***[co-lead]***
Associate Director, Environmental Science
ILSI Health and Environmental Sciences Institute (HESI)
1156 15th Street, NW, Suite 200, Washington, DC 20005 USA
1-202-659-3306 x183
membry@hesiglobal.org

James Armitage, PhD
President & Principal Investigator, AES Armitage Environmental Sciences, Inc.
15-110 Mary St W, Whitby, ON, Canada
+1 416 906 1274
James.armitage@utoronto.ca

Karla Johanning, PhD
President, KJ Scientific and KJ Scientific GmbH
111 West Cooperative Way Suite 200, Georgetown, TX 78626 USA
1-512-590-0080
karla.johanning@kjscientific.com

Heike Laue, PhD
Senior Research Scientist, Biosciences - In vitro Toxicology
Fragrances S&T / Ingredients Research
Givaudan Schweiz AG, Überlandstrasse 138, 8600 Dübendorf, Switzerland
+41 44 824 2269
heike.laue@givaudan.com

Ester Papa, PhD
Associate Professor, University of Insubria
Via J.H. Dunant 3 - 21100 Varese, Italy
+39-0332421552
ester.papa@uninsubria.it

Alessandro Sangion
PhD Candidate
University of Insubria
Via J.H. Dunant 3 - 21100 Varese, Italy
alessandro.sangion@uninsubria.it

Liisa Toose, MSc
Research Associate, ARC Arnot Research & Consulting
86851 Perth Road 178
RR#2 Wroxeter, ON, Canada1-705-957-8876
Liisa.toose@gmail.com

Annex 1: Instructor bios

Jon A. Arnot, PhD

Dr. Arnot is the President of ARC Arnot Research & Consulting and an adjunct professor in the Department of Physical and Environmental Science and in the Department of Pharmacology and Toxicology at the University of Toronto. He has 17 years of research experience in the development, application, and evaluation of databases, methods and models to assess the exposure, hazard, and risk of organic chemicals to humans and the environment. His research has focused on the application of high-throughput screening methods for prioritizing chemicals for risk assessment. Dr. Arnot holds a PhD in Environmental and Life Sciences from Trent University, an MSc from Simon Fraser University and a BSc from the University of Alberta. He is the principal investigator or co-investigator of various international projects including collaborations in the United States, Europe, and Canada. He has co-authored over 60 peer-reviewed publications and more than 50 technical reports for governments and the chemical industry.

Dr. Arnot has coordinated and participated in various workshops and training sessions with competent authorities including: Bioaccumulation Assessment (Society of Environmental Toxicology and Chemistry Short Course; European Chemicals Bureau, Joint Research Commission; European Food Safety Authority; European Chemical Industry Council, European Chemicals Agency), Long-Range Chemical Transport Assessment (Pesticide Management Regulatory Agency, Health Canada), Bioaccumulation and Human Exposure Assessment Models, Physical-Chemical Properties (Health Canada and Environment Canada), Exposure and Risk Assessment (NATO Advanced Study Institute, Sofia, Bulgaria). Dr. Arnot served on the National Academies of Sciences, Engineering, and Medicine Committee on Incorporating 21st Century Science into Risk-Based Evaluations (2015-2016) and is a member of the Canada's Chemicals Management Plan Science Committee (2017 – 2020). He is member of the Society of Environmental Toxicology and Chemistry (SETAC), International Society for Exposure Science (ISES), Society of Toxicology (SOT) and the American Chemical Society (ACS). He was the recipient of the James M. McKim III Innovative Student Research Award (2008) from the International QSAR Foundation to Reduce Animal Testing and the Society of Environmental Toxicology and Chemistry (SETAC) Best Student Paper Award (2009).

Michelle R. Embry, PhD

Dr. Embry received her PhD in toxicology in 2004 and BS in Biology and Environmental Science and Policy in 1998 from Duke University. She is currently the Associate Director of Environmental Science at the Health and Environmental Sciences Institute (HESI), where she provides leadership, technical direction, and guidance to varied, multi-stakeholder, collaborative committees on topics related to risk assessment and environmental protection worldwide. Prior to joining HESI in 2006 she was an ecological risk assessor at the USEPA's Office of Pesticide Programs. She has expertise in both human health and ecotoxicology, with an emphasis on integrated approaches and alternative methods.

Her current project portfolio includes projects related to ecological and human health risk assessment, and she is the manager of the Risk Assessment in the 21st Century (RISK21) Technical Committee, which developed a scientific, transparent, and efficient approach for human health risk assessment, including a web-based tool that has led to outreach and training activities on risk assessment approaches worldwide. Dr. Embry is a core member of the Health Canada (HC) and Environment and Climate Change Canada's (ECCC) Chemicals Management Plan (CMP) Science Committee (2017 – 2020). She was an elected member of the SETAC North America Board of Directors (2014-2017), chair of the SETAC Global Partners Advisory Committee (2014 – 2017), and a member of the SETAC Bioaccumulation and Animal Alternatives Interest Group Steering Teams. She is a full member of the Society of Toxicology and a member of the Risk Assessment and Mixtures Specialty Sections.

James Armitage, PhD

Dr. Armitage received his Ph.D in 2009 from Stockholm University. His PhD research was focused on the global-scale fate and transport of perfluoroalkyl acids (PFAAs) and it received the 2009 Sigrid Arrhenius stipendium (Best Ph.D thesis in the Sciences). He is currently a Research Associate working with Prof. Frank Wania at the University of Toronto at Scarborough (UTSC) and also the President/Principal Investigator of AES Armitage Environmental Sciences. His Master's research included the development and evaluation of a terrestrial bioaccumulation model for POPs. More recently, he was the lead author of a paper entitled, "Development and evaluation of a mechanistic bioconcentration model for ionogenic organic chemicals in fish", which was nominated as a Top Paper of 2013 in the journal Environmental Toxicology and Chemistry. He has conducted various training courses for competent authorities (Health Canada and Environment and Climate Change Canada). He is member of SETAC.

Karla Johanning, PhD

Dr. Johanning has dedicated her professional life to study different aspects of environmental biology and ecotoxicology in relation to human and environmental health. Dr. Johanning's primary research interest is in vitro metabolism and its application to determine fish bioaccumulation potential of chemicals. She has worked in both academic and industrial settings. In 2012 she incorporated KJohanning Consultancy advising the chemical industry in the use of a new technology, including the trout in vitro metabolism assay, an alternative method to assess bioaccumulation potential. Dr. Johanning is also an active member of the ILSI/HESI Bioaccumulation Subcommittee and was also a member of the ring trial, where trout liver S9 fraction and hepatocytes are used to test metabolism and assess bioaccumulation.

Dr. Johanning has provided professional training courses at SETAC on the use of trout in vitro metabolism assay. She worked for several years at Life Technologies/Invitrogen (now Thermo Fisher Scientific) and CellzDirect as a Study Director responsible for overseeing drug metabolism studies, and leading an emergent ecotoxicology unit. Dr. Johanning coordinated the activities for production of trout liver fractions (S9 and microsomes) and cryopreserved hepatocytes. She received her M.Sc. from the Dept. of Aquaculture and Fisheries and her Ph.D. from the Dept. of Zoology from the University of Rhode Island where as part of her research she studied biochemical/physiological parameters in her research using Atlantic salmon and tilapia. She did post-doctoral medical research in the Dept. of Biochemistry at the Louisiana State University Medical Center and at the Tulane University Cancer Center in the Medical School. She earned her B.S. degree (Zoology and Marine Biology) from the University of Costa Rica in her native country of Costa Rica. Karla is also an Adjunct Visiting Professor at Nicholls State University in Louisiana. She is a member of SETAC.

Heike Laue, PhD

Heike Laue is a Senior Research Scientist at Givaudan Schweiz AG, an international company based in Switzerland which is the global leader in the fragrance and flavor industry. As part of the In Vitro Molecular Screening (IMS) group she is working on in vitro metabolism to study the bioaccumulation potential of fragrance ingredients in the context of REACH registrations and as part of the new molecules program. Another focus of the work is on the toxicology of fragrance molecules by studying the in vitro metabolism in animal hepatocytes compared to humans. Prior to Givaudan, Heike worked as a Senior Research Scientist and Group Leader in a biotechnology company focused on research and development of antimicrobial agents. She did post-doctoral research at the Danish Technical University on bacterial biofilms and at Stony Brook University / New York in biochemistry. She earned her Ph.D. at the University of Konstanz in microbiology, microbial ecology and molecular medicine. She is a member of SETAC.

Ester Papa, PhD

Ester Papa, has been working as senior researcher, assistant Professor and aggregate Professor since 2007 at the Department of Theoretical and Applied Sciences of Insubria University (Varese, Italy) in the QSAR Research Unit in Environmental Chemistry and Ecotoxicology. In spring 2017 she obtained the

habilitation to professorship in Environmental Chemistry, with upgrade to associate professor starting from October 2017. Her research activity is focused on the application of chemometric methods and modelling approaches to study several topics related to human health, environmental chemistry and ecotoxicology, and drug design. Dr. Papa is an expert in the development and validation of models based on Quantitative Structure-Activity relationships (QSAR) to predict toxicological and ecotoxicological endpoints for conventional and emerging pollutants, industrial chemicals and nanoparticles. This activity includes studies regarding the use of chemometric methods to prioritize and safely design chemicals, and the integration of QSAR models within risk assessment frameworks. Dr. Papa is registered as an Expert in the CORDIS database (European Commission). As such, she has been a reviewer for the inclusion of QSAR Models Reporting Formats (QMRF) in the QMRF repository created by the Computational Toxicology Group of the IHCP-JRC (EU Commission) (2014).

Among the main research topics addressed by Dr. Papa in the last 15 years there are: the bioconcentration and biotransformation of organic chemicals in fish and humans, the prediction and prioritization of persistent, bioaccumulative and toxic chemicals (PBTs), the prediction of physico-chemical and (eco)toxicological properties of emerging, and the study of biological activities and partitioning properties of heterogeneous nanoparticles. Additionally, she collaborated on the development of the software for QSAR model development and validation QSARINS (2012). Dr. Papa has published about 60 papers on QSAR modelling in international journals, peer reviewed and more than 150 contributions to international meetings in the field of Environmental Chemistry and Computational Chemistry.

Liisa Toose, MSc

Liisa Toose is an independent research consultant with over 15 years of experience developing, applying and evaluating models for chemical fate, exposure and risk. She completed her Master's research at Trent University with the Canadian Environmental Modelling Centre in 2005. There she developed a global scale fugacity model of chemical fate and a method for predicting the fate of speciating chemicals, including mercury, acids and bases in environmental media. Since then, Ms. Toose has been involved with various modelling projects in collaboration with ARC including the development and programming of the RAIDAR model the Bioaccumulation Assessment Tool (BAT). She is a member of SETAC.