LRI work programme: recent and relevant activities (ENV)

Dr Bruno Hubesch
LRI Programme Consultant
1. LRI global effort, strategy & key Q’s
2. Process flow LRI
3. New projects from 2018 RfPs
4. Other LRI projects relevant for emerging topics and ECETOC activities
1. THE LONG-RANGE RESEARCH INITIATIVE: A GLOBAL COMMITMENT

- Integral part of Responsible Care (RC) and Global Product Strategy (GPS)
- A global effort under ICCA:
  - American Chemistry Council (ACC)
  - Japan Chemical Industry Association (JCIA)
  - European Chemical Industry Council (Cefic)
LRI-ICCA GLOBAL RESEARCH STRATEGY

- Strategy revised in July 2018
- Funding research projects in 3 priority areas:
  - Innovating chemical testing
  - Understanding everyday exposures to chemicals
  - Translating research outcomes for product safety
- LRI-ICCA research portfolio: https://www.icca-chem.org/icca-long-range-research-initiative/
- Cefic LRI: www.cefic-lri.org
SCOPE: CEFIC-LRI KEY QUESTIONS

1. **Omics / 21st Century Toxicology:** How to link information at molecular level to health impacts and interpreting results for meaningful decision making?

2. **Predictive tools for health impact:** What are pragmatic approaches for reducing complexity, whilst maintaining robust predictions of health effects?

3. **Combination effects:** How to identify combination effects scenarios of concern?

4. **Eco-systems approach:** Which new concepts enhance ecological relevance of risk assessment?

5. **Real life Exposure:** Which predictive, validated exposure scenarios apply to assessing environmental stressors?

6. **Comparative assessment:** How to interpret impact of health and environmental stressors?
WE PROVIDE FUNDING OPPORTUNITIES TO PUBLIC & PRIVATE STAKEHOLDERS

CEFIC-LRI REQUEST FOR PROPOSALS

Project grants on chemical safety assessment

3 500 000 €

- 250+ projects since the creation of Cefic-LRI
- 200+ experts on risk assessment issues

CEFIC-LRI INNOVATIVE SCIENCE AWARD

A stepping stone for future scientific leaders

100 000 €
IT TAKES A TEAM

- LRI Internal Team
- LRI External Scientific Advisory Panel (ESAP)
- Monitoring Scoping meetings
- Project definition
- Funding
- Dissemination
2. CEFIC-LRI PROJECT PROCESS FLOW

**IDEATION**
- ICCA and Cefic-LRI strategy and key questions
- Recommendations from previous LRI projects

**RECOMMENDATION**
- External Science Advisory Panel (ESAP)
- ECETOC LRI Human Health & Environmental Sciences Review and Scoping Meetings
- ECETOC expert teams, task forces, work groups
- Cefic Issue Team (EMSG, MIAT,...)
- Others (member companies, Cefic sector groups)

**DECISION**
- LRI Management Team (+ Cefic Innovation Executive Director)
- Issue Team prioritisation (2 meetings: March + May)

**ENDORSEMENT**
- Cefic Innovation Programme Council (followed by public launch Mid-June)

Main channel for project ideas
Key validation steps

- January - February
- March to May
- June
THE CEFIC-LRI PROJECT FUNDING PROCESS

June
- Request for Proposals (RFPs)
  - LRI Website

August
- Expression of Interest (EoI)
  - LRI Secretariat

November
- Results announcement

September
- Proposals evaluation and selection
  - Selection committee

January
- Research Agreement
  - LRI
  - Leading research institution

March
- Research project starts
  - Leading research institution

LRI – 20 YEARS OF LRI ADVANCEMENTS IN RISK ASSESSMENT
ECETOC’S ROLE IN THE CEFIC LRI PROGRAMME

**ECETOC**
- Review & Scoping meetings
- RfP drafting
- Selection panels
- Monitoring

**Cefic LRI**
- Project definition
- Funding
- Dissemination

**JCIA LRI**

**ACC LRI**

**Cefic LRI External Scientific Advisory Panel**
3. New projects from 2018 RfPs
## 2018 RfP LRI new projects: selected environmental research teams

<table>
<thead>
<tr>
<th>Project title</th>
<th>Code</th>
<th>Cost</th>
<th>Timing</th>
<th>Selected team</th>
<th>Kick-off meeting</th>
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</table>
| SNAPFISH “Searching for refiNed in vitro Approaches to Predict bioconcentration in FISH | ECO47| 310k  | 2 y    | Dr Kilian Smith  
RWTH Aachen University  
Institute for Environmental Research, DE                                                           | TBD             |
| Nano2Plast – Extending nanoparticle models to open source models of the fate and transport of microplastic in aquatic systems | ECO48| 220K  | 2 y    | Prof Matthew MacLeod  
Stockholm University  
Department of Environmental Science and Analytical Chemistry, SE                                  | TBD             |
| Microplastic Effect Thresholds for Aquatic Species (METAS)                      | ECO49| 460K  | 3 y    | Prof Albert Koelmans  
Wageningen University, NL                                                                            | TBD             |
| Incorporating spatial and seasonal variability in community sensitivity into chemical risk assessment (GETREAL) | ECO50| 500K  | 3 y    | Prof Ralf B. Schäfer  
The University of Koblenz-Landau, Institute for Environmental Sciences, DE                     | TBD             |
ECO47: SNAPFISH: Searching for refined in vitro Approaches to Predict bioconcentration in FISH
ECO47: IVIVE for BIOACCUMULATION

- 

  • Researcher team: Dr Kilian Smith RWTH Aachen University, Prof Kai-Uwe Goss, UFZ Leipzig

  • Monitoring team: tbd
  • Budget: about 400k €
  • Duration: 3 years
  • Collaboration under review
ECO47: OBJECTIVES

- Improving the reliability of measured HEP and S9 *in vitro* metabolic rates
- How enzymatic turnover is impacted by differences in chemical availability between the media used in *in vitro* assays and liver blood.
- Incorporating the above experimental information to improve existing IVIVE and other BCF prediction models

- Work package (WP) overview summarizing the main objectives of the Nano2Plast project
ECO48: NANO2PLAST WORK PLAN

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

- Researcher team: Prof. Matthew MacLeod & Dr. Antonia Praetorius
- Monitoring team: tbd
- Budget: 219 536 €
- Duration: 24 months
ECO48: LAY SUMMARY – Adapt & extend fate models for nanoparticles to microplastics

**Nano2Plast Models**

- New model framework for microplastic fate & transport in rivers
- Predicted environmental concentrations (PEC) at the local (river) and global ocean scale

Existing models for nanoparticles

Integrate & adapt to the oceans of the global-scale multimedia contaminant fate model BETR

Global

Fill crucial data & knowledge gaps for microplastic exposure and risk assessment
ECO48: RESULTS

• Expected results of Nano2Plast:
  • **Model toolbox** for microplastic fate and transport assessment in aquatic systems (open source, modular & easy to use)
  • **Regional & global application** of new model framework → river model & “microBETR Global”
  • Predicted environmental concentrations (PECs) for microplastics to **inform risk assessment**
  • Novel insights into drivers of microplastic fate, dominant transport pathways & sinks, microplastic exposure categorisation
ECO49 METAS

Microplastic Effect Thresholds for Aquatic Species (METAS)
ECO49: Microplastic Effect Thresholds for Aquatic Species (METAS)

• Researcher team: Prof Albert Koelmans, Wageningen University (lead),

• Monitoring team:

• Budget: 400 k€

• Duration: 4 years

• Phase I: litt review, Phase II (for approval): experimental work
Figure 1. Scheme of hypothesised mechanisms affecting microplastic exposure and effects. At low dose, intrinsic physical-chemical properties affect exposure and (for some particle types), possibly intrinsic toxicity. At higher dose, extrinsic properties like particle characteristics and species traits drive adverse effects of microplastic.
Overall aim of METAS is:

- **to provide guidance on rational testing methods** for microplastic particles including quality assurance,
- **to assess effect thresholds for aquatic organisms** using these methods,
- **to understand which are the most important factors affecting thresholds**
- **to provide guidance** on the implications of the findings for the **environmental hazard and risk assessment** of microplastics.
ECO50: GETREAL
WORK PLAN

Incorporating spatial and seasonal variability in community sensitivity into chemical risk assessment
GETREAL

Researcher team: Prof. Ralf B. Schäfer, Prof. Martin Entling (both University of Koblenz-Landau), Prof. Paul van den Brink (Wageningen University), Prof. Lorraine Maltby (Sheffield University), Prof. Frederik de Laender (University Namur)

• Monitoring team: TBA
• Budget: 499,404 €
• Duration: March 2019 – March 2022
SUMMARY

- How does chemical sensitivity of organisms vary across seasons and space in Europe?
- Consequences for chemical risk assessment?
- Identification of typical assemblages and their sensitivity
- Integration of insights into risk assessment framework
4. Other projects relevant for emerging topics and ECETOC activities
iTAP
LRI ECO46

Improved aquatic Testing and Assessment of cationic Polymers
ECO46: iTAP – Improved aquatic Testing and Assessment of cationic Polymers

- Researcher team: Hans Sanderson (Aarhus Univ (PI)); Martin Hansen (AU); Anna M. B. Hansen (AU); Scott Belanger (P&G); Monica Lam (P&G); Kristin Connors (P&G); Jessica Brill (P&G); Jane Rawlings (P&G)
- Monitoring team: Frederic Palais (Solvay), Marlies Bergheim (Henkel), Philipp Hopp (BASF) and Steven Droge (Amsterdam U.).
- Budget: 352,195 Euro from Cefic LRI (+ additional >500KE partner in-kind contribution)
- Duration: Sept 2018 to Sept 2021
The overall aim of the iTAP project is to support the science-based development of methods to allow accurate and precise aquatic environmental risk assessment of cationic polymers by further developing the ECETOC bulk approach.
ECO46: OBJECTIVES

• **Objective 1) Review:** Collect and review the environmental polymer science of cationic polymers past two decades peer-reviewed and industry and regulatory data on toxicity and fate properties.

• **Objective 2) Chemical analysis and Exposure assessment:** Clarify the methods needed for analysis of cationic polymers in water. Develop simplified analytical methods. Assess what this means for the exposure assessment and model domain of EUSES in more realistic ‘nano-cosm’ testing with humic acid and particles in the test water.

• **Objective 3) Aquatic toxicity:** We will assess dozens of different combinations of polymers and water types in algae, daphnids, and fish embryos and develop novel predictive models.

• **Objective 4) Aquatic risk:** We will address environmental risks through description of the bulk approach (ECETOC, 2003).
ECO46: RESULTS

- Selection of relevant cationic polymers:
  - PQ-6
  - PQ-7
  - PQ-10
  - PQ-16

- Review protocol ready (Deliverable 1)

- Experimental prioritization procedure is ready:
  - Literature review results
  - QSAR screening
  - MicroTox testing
  - Range finding acute daphnid tests

EU industry project focuses on assessment of cationic polymers

The EU chemical industry has launched a three-year project to improve environmental risk assessment of cationic polymers, which are widely used in hair products such as shampoos and conditioners.

The "Improved aquatic testing and assessment of cationic polymers" (ITAP) project, launched in September, brings together Aarhus University in Denmark and global consumer products giant P&G.

The polymers combine two contrasting elements – a positive charge and a long hydrophobic chain – and the resulting dichotomy typically provides unusual behaviours in water, particularly in interfacial regions. A 2000 BASF study of those used in hair products suggested that they stick to the hair and the chains form hydrophobic loops that provide a "conditioning" effect by reducing friction between strands.

The project aims to "lay the foundation for regulatory acceptance based on improved methods" and add significant gaps in the knowledge base.

One of the challenges is that the polymers are typically large and not expected to pass biological membranes, making toxicity testing problematic. Another is that they are expected to interact with the outer membranes of aquatic organisms and thereby affect their functionalities. This behaviour makes it hard to describe the dose–response relationship.

The team will assess a group of closely related but "understudied" model cationic polymers widely used in industry. They will address several OECD test guidelines, including:

- the freshwater alga and cyanobacteria growth inhibition test, TG 201;
- the Daphnia sp acute immobilisation test, TG 202;
- the Daphnia magna reproduction test, TG 211; and
- the fish embryo acute toxicity test, TG 236.

The project is funded by a €350,000 grant from the European Chemical Industry Council's (Cefic) Long-range Research Initiative (LRI) and is led by Hans Sanderson at Aarhus University.
OVERALL APPROACH DEVELOPMENT OF AN ALTERNATIVE TESTING STRATEGY FOR THE FISH EARLY LIFE-STAGE TEST FOR PREDICTING CHRONIC TOXICITY: ASSAY VALIDATION

Molecular Initiating Event → Key Event → Key Event → Key Event → Adverse Outcome

In chemico assays → Zebrafish embryo tests → Fish Early Life Stage tests

Predict in vivo effects → Predict in vivo effects
ECO20/20.2 OUTCOME: THYROID AOP NETWORK

- TPO inhibition assay
  - TH synthesis decreased
  - TH activation decreased
- TPO inhibition
  - T4 in serum decreased
  - T3 in serum decreased
- DIO1/2 inhibition
  - mRNA thyroid related genes
  - Serum T3 measurement
- DIO1/2 inhibition assay
  - FET: posterior swim bladder
  - FET: swimming behaviour
- FELS: anterior swim bladder
  - Anterior swim bladder inflation reduced
  - Posterior swim bladder inflation reduced
- FELS: swimming behaviour
  - Swimming performance reduced
  - Young of year survival reduced
  - Population trajectory decreased

LRI – AN AOP-BASED ALTERNATIVE TESTING STRATEGY FOR PREDICTING CHRONIC TOXICITY IN FISH
Investigations on the bioconcentration of xenobiotics in the freshwater amphipod *Hyalella azteca* and inter-laboratory comparison of a new BCF test protocol.
ECO40: Alternative methods for bioaccumulation testing

Bioconcentration studies (according to OECD TG 305)

BCF

BCF in vitro

Modelling

Biotransformation rate (BTR)

Liver in vitro systems
- Primary cell suspension
- Subcellular fractions (S9)

Biomagnification studies (according to OECD TG 305)

BMF

Elimination rate constants (ko)

Hyalella BCF test

Bioaccumulation assessment

Biotransformation pattern

= New approach  = State of the art

LRI – Investigations on the bioconcentration of xenobiotics in the freshwater amphipod *Hyalella azteca* and inter-laboratory comparison of a new BCF test protocol
ECO40: Biotransformation comparison

H. azteca (3)
- Glucose conjugation
- Malonyl-glucose conjugation
- Taurine conjugation

Fish hepatocytes (1)
- Glucuronide conjugation

Both (11)
- Hydroxylation
- Hydrolysis
- Reduction
- Demethylation
- Deethylation
- Methylation
- Dehydrogenation
- Loss of imidazole ring
- Loss of propyl side chain
- Sulfate conjugation
- Glutathione conjugation

in vivo

in vitro

LRI – Investigations on the bioconcentration of xenobiotics in the freshwater amphipod *Hyalella azteca* and inter-laboratory comparison of a new BCF test protocol

29/01/2019
Results from Part I
1 Azoxystrobin
2 Prochloraz
3 Terbutryn
4 Trifloxystrobin
♦ Data from Schlechtriem et al. 2019

Hyalella BCF data seem to be predictive of bioconcentration in fish

*Hyalella azteca* bioconcentration test concept submitted to OECD TEST GUIDELINES PROGRAMME (SPSF)
Potential ring test ECO40.2
ARC.5: Using Fugacity Ratios to Inform Bioaccumulation Assessment

Background

• Merits and limitations of B and T metrics and criteria (e.g., Maeder et al., 2004, Gobas et al., 2009, etc)
• The fugacity ratio approach (Burkhard et al., 2012) uses multiple lines of evidence from lab and field B endpoints (e.g., BCF, BMF) in a weight of evidence (WOE) approach for B assessment
• Increasing regulatory interest to use invertebrate B data for B assessment
• Bioaccumulation Assessment Tool (BAT) provides a WOE framework including fugacity ratio output; however, the capacity for including B data for invertebrates in the current version of BAT is limited

General approach

• Expand BAT to include more lab and field derived B metrics for invertebrates (i.e., BCF, BMF, BAF)
• Apply BAT as a case study for various chemicals to highlight the fugacity ratio approach for B assessment
• Develop and apply a model to effectively demonstrate the bias in current B and T criteria for high Kow chemicals

Comparing Laboratory and Field Measured Bioaccumulation Endpoints

Lawrence P Burkhard,* † Jon A Arnot,‡ Michelle R Embry,§ Kevin J Farley,∥ Robert A Hoke, # Masaru Kitano, ∥∥ Heather A Leslie, ‡ Guillaume R Lotufo, §§ Thomas P Parkerton, || Keith G Sappington, ## Gregg T Tomy, ∥∥∥ and Kent B Woodburn ‡‡
### Scientific Impact

- Fugacity ratio approach and more BAT case study applications will facilitate:
  - Scientific evaluation of invertebrate lines of evidence in a WOE approach (e.g., Hyalella / Daphnia lab BCF tests; mollusc BAFs & BCFs; field BMFs & BAFs)
  - Focus on biomagnification, rather than bioconcentration
- Exploring the underlying toxicokinetics (TK) in current B and T criteria in a holistic manner will highlight the biases in hazard categorization against high Kow chemicals and promote the biomagnification approach
- Provide a scientifically-defensible, unbiased approach for B and T assessment criteria

### Policy Impact

- Continued development and application of the BAT in communication with regulatory community (ECHA, ECCC, USEPA, others)
- Continued promotion of a WOE approach for B assessment with multiple stakeholders

### Relationship with Previous Cefic-LRI Work, Timeline and Resources

- Previous Cefic-LRI projects: ECO.16, ECO.30, ECO.33, ECO.34, ECO.40, ECO.41, ECO.44, ARC3 (BAT)
- Short-term (~ 1 year); 100K Euro
Proposal ranked 6th at 2018 meeting:
Analytical methods to assess human exposure to plastic particulates in food and the indoor environment

- **Objectives**
  i) Develop analytical method(s) to detect, identify and quantify micro- and ultrafine plastic particles of diverse chemical makeup in biological and abiotic matrices
  ii) Build the evidence base for realistic human exposure scenarios to small plastic particles
  iii) Systematically, critically assess the safety of plastic particulate exposure to human health

- **Budget/duration**
  4-5 years (€100K per year)

- **Status**
  LRI IT decided in April 2018 to delay in view of ongoing activity
Proposal ranked 4th at 2018 meeting: Improved regulatory acceptability of Fish Embryo Test

- **Objectives**
  
i) Propose a quantitative (preferred) or qualitative WoE for FET as a replacement to AFT
  
ii) Determine the likelihood of prediction for major classes of compounds and MoA
  
iii) Evaluate the reliability of both AFT and FET studies and impact on WoE

- **Budget/duration**

  2 years (€125K per year)

- **Status**

  Not considered by LRI IT Mar 2018. ECETOC SC advised that more info needed on status.
  Call mid-2018 with those who indicated interest during 2018 meeting (industry and regulators). Agreed that:
  
  - The proposal represents important and timely research, relates to a request from ECHA to industry (May 2017 ECHA/UBA WS), and is of relevance to Europe and worldwide.
  - Clarified that invert data and threshold approach would be considered in the WoE

  Next step – Presentation to LRI IT
GOING FORWARD: OPPORTUNITIES

- Diminishing weight of scientific knowledge in decision-making
- Acceleration of political processes – science is too slow