CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Title and Code Number:
A toxicokinetic mammalian modelling framework for B assessment – **LRI ECO44**

Background
To date, bioaccumulation (B) assessment has focused on information regarding the bioconcentration of chemicals from water by fish. However, the United Nations Stockholm Convention on Persistent Organic Pollutants, REACh legislation in Europe and legislation in Canada and the US also recognize the importance of bioaccumulation in species other than fish and biomagnification of chemicals from food-sources. Bioaccumulation of chemicals in mammals is of particular interest because of its relevance to both environmental and human health. Various agencies including ECHA are currently using mammalian bioaccumulation data in chemical evaluations. Guidance on how to use and evaluate information from mammalian studies for B assessment is urgently needed. Furthermore, the phasing-out of live animal studies in Europe and other countries and the emergence of *in-vitro* and *in-silico* approaches and new guidelines for bioaccumulation testing by the OECD require novel approaches to B assessment. An important part of a mammalian oriented B assessment approach is a toxicokinetic framework that can make use of information from a variety of available sources including laboratory based *in-vivo* and *in-vitro* studies and field studies. The main purpose of the toxicokinetic modeling framework is to evaluate chemicals for B in screening and risk assessments and to conduct species-to-species extrapolation and food-web bioaccumulation assessments. This toxicokinetic framework should be science-based and provide information relevant to current regulatory needs and the improvement of bioaccumulation assessment through new science-based approaches. The toxicokinetic framework can build on or adapt existing kinetic modeling frameworks (e.g. PBPK models for rats or mice) used in mammalian toxicology in the pharmaceutical, medical, and pesticide sciences. The framework should be capable of conducting B assessments under dynamic and equilibrium conditions and consider the potential benefits of benchmarking. The toxicokinetic modeling frameworks for B assessment in mammals and fish should be scientifically consistent and mutually supportive. For a toxicokinetic mammalian modeling framework to be credible and useful, it needs to be thoroughly tested and evaluated for uncertainties, sensitivities and domain of applicability and disseminated in the scientific literature.

Objectives
The project's objectives are to:
1. Develop a toxicokinetic mammalian modelling framework for B assessment of chemicals based on absorption, distribution, metabolism and excretion kinetics

that can treat information from *in-vivo* animal studies, hepatic and gastro-intestinal biotransformation bioassay and protein-binding studies to generate innovative B metrics and/or assess regulatory bioaccumulation metrics currently considered relevant, such as the depuration half-life time, BMF and TMF.

2. Test the toxicokinetic mammalian modelling framework for its ability to accurately assess the bioaccumulation behaviour of chemicals based on a variety of potentially available input data (e.g. depuration rates, dietary uptake efficiencies, *in-vitro* biotransformation rates in liver S9 and/or microsomal preparations, and/or intestinal preparations, concentrations of chemicals in blood, *in-vivo* biotransformation rates).

3. Investigate the uncertainty and applicability domain of a toxicokinetic mammalian modelling framework for B assessment of chemicals

4. Investigate the application of data from a toxicokinetic mammalian modelling framework in a weight-of-evidence approach to B assessment.

5. Consider guidance and advice from regulators to ensure that the toxicokinetic framework meets the needs of the regulatory community.

Research should take into account ongoing activities in the area fill apparent gaps not covered by the existing work and establish an integrated model approach building on this work.

Deliverables

Develop and test a toxicokinetic mammalian modelling framework for B assessment of chemicals, including generation of regulatory bioaccumulation metrics.

The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography. It is expected that the findings will be developed into at least one peer reviewed publication, following poster(s) and presentation(s) at suitable scientific conference(s).

Cost and Timing

Start in January 2018
Duration: 2 years
Budget: in the order of €250k

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Partnering/Co-funding
Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package.

Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination
Applicants should provide information on the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be laid down.

DEADLINE FOR SUBMISSIONS: 31 August 2017

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications.