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

Request for Proposals (project code LRI-B11)

Title:
Development of an integrated modelling approach to predict internal exposure to chemicals

Background

Several LRI-sponsored projects have considered the relation between external exposure and internal doses/concentrations of chemicals in humans (i.e. level and time course at the target organ or in blood plasma) to better address risks from secondary poisoning or workplace exposures. Those included the intake fraction concept (B4 – Jantunen *et al*), the development of toxicokinetic models to predict tissue levels and better understand internal dose response (B2.7 – Loizou *et al*), biological monitoring of exposure (D1.1 – Jakubowski *et al*, Watson *et al*), and two projects on the identification of relevant metabolites and their relation to human biomonitoring (HBM) results (*in vitro* metabolism and MoA data in combination with kinetic modelling; HBM3 – Blaauboer *et al*), and on the tools needed to achieve a more reliable interpretation of HBM data (tiered set of modelling tools for derivation of HBM guidance values; HBM2 – Jongeneelen *et al*, Bartels *et al*), and an ongoing project on the intra- and inter-variability of HBM spot samples (HBM4 – Smolders *et al*).

However, an integrated approach of predicting human internal exposure levels is still lacking. This would contribute to a more accurate risk assessment, better understanding of the contribution of different exposure routes and sources of exposure to total body burdens and to a better understanding of the impact of long-term low-level exposures to persistent chemicals. A recent IHCP [a]-ECETOC Workshop on "Exposure and Risk Assessment of Chemical Mixtures in Consumer Products" [b] also recommended research along these lines.

Objective

The objective of this project is to develop an integrated methodology, based on modelling of fate, transport and toxicokinetics, to determine better estimates of internal exposure of different populations over the life-cycle of a substance. The results should be validated against available results of reliable HBM studies.

In a first Tier the approach could be applied to the more defined exposure situation at workplaces for substances for which biological monitoring results as well as external exposure data are available, preferably by inhalation and the dermal route. Sources of information can be the different databases developed under the HETRA LRI programme. In this context the contribution of different routes of exposure to the total body burden should be evaluated as well and if possible be related to physical chemical properties of substances.

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[a] Institute for Health and Consumer Protection
[b] JRC, Ispra, Italy: 29-30th January 2009

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The second Tier should consider secondary exposure of humans in particular to persistent chemicals. Existing HBM data in human plasma and breast milk could be evaluated using comparison with integrated model predictions, possibly by a combination of advanced environmental fate modelling and PBTK calculations. It should be evaluated if it is possible to differentiate between HBM results representing steady state levels and those rather reflecting an acute exposure situation by comparing time trends and modelling predictions.

Scope
It is expected that the methodology would be developed using a representative number of chemicals and would include defining applicability domains and uncertainty analysis. It is expected that the findings will be reported and published in peer reviewed publications. This project would be expected to complement ongoing European Commission (including IHCP) and other supported activities in the area. The successful research group would liaise with and take account of the findings and outcomes of such other work.

Cost & timing
2 years, € 300 k

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.

DEADLINE FOR SUBMISSIONS: August 31, 2012
Please see www.cefic-lri.org for the project proposal form and further guidance for grant applications.