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

Title and Code Number:
Development of tiered testing strategies: evaluation of (Q)SAR prediction models based on *in vitro* and *in vivo* metabolism – Q2

Background
Knowledge of the metabolism of chemicals is an important requirement to comply with REACH. This includes both qualitative and quantitative information, i.e., structures of metabolites and rates of concurrent pathways, with a particular focus on the situation in humans. The evaluation of these properties should follow a tiered approach starting with a review of existing literature and data, including data for related chemicals. The next tiers would include a (Q)SAR prediction and simple *in vitro* screening assays, followed by the use of more complex *in vitro* three-dimensional models. The highest tiers are testing in lower species and finally the traditional animal tests.

For REACH extensive data on the toxicological properties of chemicals and their potential metabolites will have to be acquired. In this context alternative test methods in line with the 3R principles (refinement, reduction, replacement) become increasingly more important to improve animal welfare. Besides *in vitro* test methods, *in silico* methods such as QSARs create further prospects for reducing animal testing.

A number of models and programmes have been developed to predict metabolic pathways on the basis of structural components, some of which are commercially available. The current limitation of (Q)SAR models resides in that they are biased to consider a far greater number of metabolites than actually observed. Prioritization based on these data risk to end in erroneous forecasts or may put too much emphasis on one of the two phases in metabolism (e.g. conjugation reactions, detoxification). However, validation is limited to *in vitro* data, and results of comparison between models regarding predictive value are not available in a comprehensive manner. This gap of knowledge should be filled.

Objectives
This proposal is intended to enhance the predictive power of simulated *in vitro* metabolism by using metabolically active *in vitro* systems as well as published and proprietary *in vivo* metabolism data to clarify the accuracy of prediction of available tissue specific (Q)SAR metabolite prediction models. One potential outcome is the definition of a set of principles as guideline how to conduct and/or to constrain the (Q)SAR prediction. Where metabolite prediction results in erroneous prediction, a correction of the algorithms and improvement of the model could be sought in cooperation with the modeller (e.g. TIMES / LMC).

Scope
This RfP is addressed to laboratories that are familiar with (Q)SAR and/or metabolite profiling. The strategy is to connect *in vitro*, *in vivo* and *in silico* alternative methods to develop an intelligent testing strategy to identify chemicals with the potential to cause toxic effects. Collaborative work might be needed and respective projects are welcome. The aim is a comparison of various models for their predictive value for *in vivo* metabolism. The analysis should be based on a selection of chemicals of different

structural classes. The benchmark should ideally be the metabolism in humans, but data available from rats could constitute a first step.

The Proposal should state

- The models to be used
- The chemicals to be investigated
- The data on metabolism to which the prediction is confronted
- The gaps of knowledge and the approach to fill them
- The quantitative and statistical criteria to analyze the fits
- The new physicochemical descriptors used for modelling metabolism data
- The data mining methods being used

Short interim reports on progress are required at 6-monthly intervals. It is expected that the findings will developed into a peer reviewed publication, following presentation at a suitable scientific conference.

Cost and Timing

Budget in the order of €150,000
Start in 2008, duration up to 24 months