INTEGRA

Integrated External and Internal Exposure Modelling Platform

(INTEGRA)

B11 - Realistic estimation of exposure to substances from multiple sources
(CEFIC Long-range Research Initiative funded project)

D1.1 DESIGN AND ORGANIZATION OF SURVEYS WITH FOCUS GROUPS FOR USER REQUIREMENTS AND APPLICABILITY DOMAIN

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A. Introduction

To identify the specific user requirements, the development process of the INTEGRA conceptual framework will benefit from an extensive consultation with potential users and stakeholders. Setting up in the early phase of the project a focus group of experts consulted through dedicated workshops will ensure this. The group comprised experts from industry (in co-operation with ECETOC), regulatory authorities (ECHA, US EPA, national authorities), and academia (members of the Eur. Com. Scientific Committees). The focus group in collaboration with the project scientific advisory board gave main directions for software development. The results of this interactive process will be translated into functional specifications and definition of the applicability domain of the INTEGRA methodology and computational platform.

More specifically, a series of international scientific events were followed and co-organised by the INTEGRA team to better embed the work of the project in the international efforts towards improved risk assessment of chemicals and reach out to the largest possible number of stakeholders with relevance to the project design. These events took place from August to October 2013 and are summarized below:

1.) Conference of ISEE, ISES and ISIAQ Basel, Switzerland 19th – 23rd August 2013.

2.) Eurotox 2013 Interlaken Switzerland 49th Congress of the European Societies of Toxicology – 1st – 4th September 2013.

3.) International Symposium on Biological Monitoring (ISBM) 9th - 11th September 2013 - Manchester.

4.) 17th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region MESAEP - September 28th to October 1st , 2013 Istanbul – Turkey.

5.) WHO Workshop on Multiple Exposure and Risks – 16th to 18th of October 2013, Bonn, Germany.

The discussions held at these events were summarized in the following sections and have been used as key stakeholder consultation input for the determination of the functional specifications and design of the INTEGRA computational platform.

B. Conference of ISEE, ISES and ISIAQ Basel, Switzerland 19th – 23rd August 2013

This was the largest conference on environment and health organized ever, bringing together three of the largest international societies active on environment and health issues. A dedicated session on advancing exposure science in the era of the exposome was put together jointly by the European Commission and NIEHS. Prof. Sarigiannis was invited to the session and the American and European projects on the exposome were presented and debated. The stakeholders agreed that it was important to integrate external

and internal exposure and the necessary analytical and modeling tools need to be developed. Time scale and lifeline issues, windows of susceptibility need to be identified to allow for more relevant exposure assessment to assess properly the health effects of environmental and consumer chemicals. Given the amount of data currently generated by high throughput systems a computational platform that allows handling data for a large chemical space and allows data sharing and collaborative work is necessary.

Specific modeling requirements include:

- integration of prior knowledge
- dynamic modeling taking time and non-linearity of effects into consideration

An issue that emerged as a key challenge to be addressed when predicting internal exposure levels is the ability of the modeling system to take into account differences in physiology that affect ADME properties of each individual. The temporal variation of exposure highlights critical facets of life and day-to-day variability that needs to be captured to allow integration of high throughput system and human biomonitoring data.

C. Eurotox 2013 Interlaken Switzerland 49th Congress of the European Societies of Toxicology – 1st – 4th September 2013

On the 1st day of the Eurotox congress, September 1, a Satellite Symposium on "New Advances in Risk Assessment" was organized by BHMF (Bo Helmstedt Memorial Foundation) to allow all participating stakeholders become informed about the most recent developments in risk assessment methodology. The INTEGRA PI, Prof. Sarigiannis, was invited to give a lecture at the Symposium regarding advances in exposure science and integration of external and internal exposure assessment of chemicals towards improved prediction of internal exposure to chemicals. In the context of the congress, which brought together high-level scientists from academia, research institutes, international organizations (WHO), regulatory agencies (ECHA), and industry executives a wide-ranging discussion on the current needs of exposure science to address the advanced challenges in risk assessment in the 21st century was held.

In-depth exposure assessment was deemed to be limited by feasibility of population studies (in particular for cancer risk assessment very large sample size of the respective population cohorts is needed). Human metabolic phenotype diversity and its association with diet and blood pressure need to be taken into account when internal exposure of chemicals is estimated.

Human biomonitoring studies may be of help in advancing exposure and risk assessment of chemicals. However, translation of concentrations of a chemical in blood or urine of individuals to external exposure dose can only be performed if the toxicokinetics is well described. Here again, the number of individuals to be sampled is a limiting factor that depends on the chemical family assessed: larger sample size is needed for rapidly metabolized chemicals, such as bisphenol A. Indeed, it was deemed that developments in PBPK modeling are likely to provide important tools by which in vitro to in vivo extrapolations can be improved, and thus, release the potential of in vitro assays for both

internal exposure and toxicity testing of chemicals. Integrating human dosimetry and exposure to advanced toxicological testing platforms such as ToxCast requires accurately enough prediction of internal dose of chemicals. ToxCast results so far show that ca. 10% of the chemicals tested on the high-throughput testing platform have in vitro biological activity at oral equivalent doses that overlap with the most highly exposed subpopulations.

Another key aspect that was highlighted by the stakeholder group was that changes in behavior and physiology occur in different life stages. Development occurs on a continuum but existing information and tools are not adequate for an exposure function that captures this change. Age bins are used as proxies to this developmental continuum. A life stage approach to exposure analysis is needed to determine the most critical windows of exposure linked to specific health outcomes. Thus, any internal exposure modeling effort should capture these features of human physiology that alter metabolic capacity and other features that modulate the actual internal dose of chemicals in the body at different life stages. Indeed, a life course PBPK is needed to support advanced exposure assessment.

In this context, uncertainty in internal exposure prediction needs to be quantified and captured by the proposed methodology in INTEGRA. The Dempster-Shafer theory (DST), an extension of generalized Bayesian inference, was proposed to quantify uncertainty in the INTEGRA estimators or predictors due to either data or model reliability. DST allows to quantitatively account for reliability and relevance of diverse multiple evidence sources, reducing thus the overall uncertainty of the estimate.

D. International Symposium on Biological Monitoring (ISBM) 9th - 11th September 2013 – Manchester, United Kingdom.

On Wednesday 11th September, a workshop on the CEFIC LRI INTEGRA project was held. The workshop focused on the identification of user requirements that will drive the technical specifications of the developed methodology and the respective computational platform.

The consensus of all stakeholders who participated in the INTEGRA workshop was that when it comes to exposure models it is advisable to start simple and gradually add complexity to the model structure to improve its performance. In this context, PBPK models are seen as the next best thing to extensive measurements in different biological fluids and tissues in humans. Sensitivity analysis would allow us to determine the most critical parameters for model performance. Model usability is also associated to the possibility to maintain live links with parameter databases that would allow model adaptation to scientific progress.

Mechanistic models allow us to approach the causal association between exposure and effect. Models need to capture as much biology or disease mechanisms as possible to be successful. There is a clear need for a metabonomic signature database that is widely accessible, since biomarker data for chronic disease are already available, but not centrally collected and managed.

Reconstruction of exposure will be the significant improvement that will come from toxicity data. If we know when concentrations cause toxicity then we can work back to reconstruct exposure. There is, however, a need to differentiate between "near" and "far field" exposure data. Near field may need more refined exposure data, where far field may be more in need of better toxicity data. The conclusion was, nonetheless, that in general we need both better and more toxicity data and better data appropriate for correct exposure characterisation.

A key problem is the misuse / misinterpretation / misrepresentation of model output by non-expert users. Thus, it is deemed that a user-friendly and transparent user interface is required for any such integrated exposure model to be widely and correctly used. Uncertainty needs to be represented in an understandable way - in this context, graphical representations of uncertainty may provide a viable solution.

The exposure models can be the same for both occupational and environmental or consumer exposure scenarios, however different parameterisation schemes are warranted in the different exposure settings. Normal populations are more sensitive than workers due to their enhanced diversity. It has to be noted that occupational exposure regulation often works with clear limit values - this is not the case with environmental exposure.

Overall, the stakeholders agreed that models do provide useful insights. Non-modellers erroneously take the modelled data with being aware of the model limitations, even though the modellers themselves understand that a model is only a representation of reality. For this reason, a "stop light" approach was proposed. If a chemical is in the "green" zone of a very simple tier 0 model, then there is no need for refinement. However, if it is in the "orange" or "red" zones, then we need to proceed to more complicated tier 1 and tier 2 models. In a nutshell, the stakeholder recommendation is to start simple and add complexity when needed, keeping in mind that the model output needs to be easy to interpret.

E. 17th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region MESAEP - September 28th to October 1st , 2013 Istanbul – Turkey

This regional conference featured a dedicated session on environment and health issues chaired by Prof. Sarigiannis, with keynote participation of Dr. Marco Martuzzi, programme manager at the WHO European Centre of Environment and Health, as well as lectures from colleagues from Harvard University. Dr. Alberto Gotti and Dr. Spyros Karakitsios (CERTH) gave presentations on elements of the INTEGRA platform and methodological concepts for predicting internal exposure to chemicals in particle form. The need for integrated exposure assessment was highlighted and the benefits of innovative internal exposure evaluation were underlined by the stakeholders.

F. WHO Workshop on Multiple Exposure and Risks – 16th to 18th of October 2013, Bonn, Germany

The workshop organized by the WHO European Center for Environment and Health brought together primarily regulators from all countries in the WHO European region. Its primary objective was to discuss the salient issues regarding properly assessing the risk on human health from co-exposure to multiple stressors. A special section of the workshop was dedicated to the issue of combined exposure to multiple chemicals in mixture. Capacity building was also a key objective of the workshop, especially with regard to managing carcinogens, mutagens, reproductive toxicants and endocrine disrupting chemicals (EDCs), as well as managing contaminated sites on the basis of the relevant risk assessment. The target audience comprised experts from regulatory authorities in the WHO–Europe member states. During the workshop the IPCS and ILSI/HESI methods and tools for regulatory use in terms of addressing chemical mixtures risk were shown. The IPCS tiered approach to combined chemical exposure was presented and the relevance of predicting internal exposure at higher assessment tiers was underlined.

Time-related aspects of exposure assessment were deemed necessary to be addressed by any exposure modeling tool, both for external and internal exposure. Information on the chemical structure of the compounds considered for combined exposure assessment, as well as hazard or other biological data (target organs, biological outcomes, intended target of each chemical) help in determining the need for combined exposure assessment. The IPCS exposure assessment approach shown at the event included the following tiers:

- Tier 0: simple semi-quantitative estimate of exposure
- Tier 1: generic exposure scenarios using conservative point estimates
- Tier 2: Refined exposure assessment, with increase use of actual measured data
- Tier 3: Probabilistic exposure estimates

The relevance and applicability of this approach was demonstrated on a family of N-methyl carbamates (insecticides), which have the same mechanism of action, thus one can assume additivity of dose to estimate the actual effect of co-exposure to them. Diet is a key exposure route. Occupational exposure can occur during application; it can be complemented by non-occupational exposure in residences through use of these insecticides on lawns, gardens or on pets.

An integrated exposure prediction modeling platform such as INTEGRA needs to consider all of the above exposure routes to address an as large as possible chemical space.

G. Conclusions

The conclusions of the different stakeholder consultations outlined above can be summed up as follows:

INTEGRA needs to cover a large enough chemical space to allow unbiased estimation of the link between exposure to chemicals and health effects. Furthermore, the computational platform and database need to be able to service large data sets and provide the possibility to users to do shared work in order to maximize the efficiency of the exposure and risk assessment process, while maintaining the confidentiality of the data incorporated in the platform to perform exposure assessment.

Differences in physiology at various life stages have to be considered; human metabolic phenotype diversity and its association with diet and blood pressure need to be taken into account for internal exposure model development. Model formulation needs to be dynamic in time and take into account non-linear physiological responses. Overall, a life course dynamic PBPK model is warranted to support integrated exposure assessment and get the most out of human biomonitoring studies. Model development must, however, be parsimonious, adding complexity only when and as needed. Uncertainty needs to be quantified and captured explicitly by the INTEGRA methodology and software.

Mechanistic models such as the ones under development in INTEGRA are needed to support causal associations between environmental exposure to chemicals and health effects. “Far” and “near field” exposure settings need to be covered by the formulation of the INTEGRA platform. However, no matter how detailed the INTEGRA model formulation might be, there is always the risk of misuse of the model and misrepresentation / misinterpretation of the results by non-expert users. Thus, transparency of computation, data and assumptions used is essential for correct use of integrated exposure modeling. Finally, it is advisable that the INTEGRA model supports the implementation of the tiered approach to chemical mixture risk assessment developed by IPCS.