# 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)**

# D6.2 WORKSHOP ON FUNCTIONAL SPECIFICATIONS AND DOMAIN OF APPLICABILITY OF INTEGRA METHODOLOGY

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## Summary of INTEGRA workshop at the ISMB meeting

A dedicated session on INTEGRA was organized and chaired by Dr. Roel Smolders (RS). The workshop was attended by 11 people (which included several INTEGRA project team members). Participants were from a range of countries including UK, US and European countries.

RS explained the aim of the INTEGRA project – a harmonised computational platform that can be used to predict internal exposure to chemicals. The platform would have two tiers – one occupational, the other environmental, which are proposed to be validated by biomonitoring studies.

The workshop was structured in that participants were asked to consider two statements and discuss / defend them. This note attempts to summarise the comments made for the various statements presented.

### Models viewed as simplification of the real world vs. the understanding that models are wrong but useful as can update to refine

The first part of the discussion focused on the effect of input data to exposure models and their effect on model validity. Models by definition are a simplification of reality. They are wrong, but useful. Parameters need to be added only when a model needs to be redefined. The key guiding principle for model development should be as follows: start simple and only add complexity to improve the model. There need to be up-to-date links with existing databases from which data needed for running the models can be taken.

A key problem to the everyday use of models for exposure assessment is the fact that the knowledge gaps are not always known, rendering thus questionable the validity of the models.

One workshop participant was critical of PBPK models – how do you validate the model, the latter may fit blood data but none has measured anything in the brain. At the same time it was suggested that PBPK modelling is done because of the lack of human data, so it basically is the next best thing. PBPK models are used because you cannot measure in the various body compartments – models are the next best thing. A viable approach to model development would be to start from empirical data and build the model to represent the experiential information.

The people's expectations from such models need to be highlighted and managed. Most modellers are rigorous, the problem is users who misuse the model, do not understand it or misinterpret/misrepresent the results. Modellers will give uncertainty about a number but a company or regulator for example will want a number. Consequently, there is a need to understand limitations of modeling. Sensitivity analysis will tell you the sensitivity of parameters such as partition coefficients. Sensitivity analysis points out where the 'weak spots' of a model lie, but uncertainty needs to be represented in an understandable (e.g. graphical) way as well.

A tiered approach, whereby a 1$^{st}$ tier starts from a simple model, and a 2$^{nd}$ tier includes more precise but more complicated and more information. Models can be looked at as building blocks

towards the development of an integrated approach to exposure assessment. There was discussion about a LRI project completed last year (DOW chemicals) – simple tier 0, tier 1 deterministic and tier 2 population based. Finally, it was made clear to all that if we have data which relate biomonitoring values with health effects then we do not need a model.

## Human biomonitoring as gold standard vs. HBM as having limitations and is as uncertain as model outcome

How does biomonitoring fit in with models? If you have HBM data and there is a link with health effects then you do not need the model. One can be as critical about biomonitoring as with models. We add complexity if we attempt to set a guideline value based on early effect outcome or real-health outcome. There are a lot of errors with toxic ranges and lots of challenges in biomonitoring data still exist. Mechanistic models allow us to approach the issue of exposure and effect. Models need to capture as much biology of disease as possible.

In any other scientific endeavour, modelling is seen as a cheap option, but not in our field. It is not just a matter of how much data is generated but also what can be made available. There is not necessarily a linear relation between exposure and effect, so one needs to be critical about extrapolating; in this context there is a lot of value in exploring in-vitro data. If a model predicts something and this is what was measured then have faith in the model.

Industry set standards that they can observe, being pragmatic. How, however, do we define an accurate biomonitoring standard? Should there be a cost / benefit analysis? Policy issues – allocate a number and then decide to set a number, set percentile. We need to also look at costs as well (ALARP). Human biomonitoring cannot be seen generally as a gold standard.

The discussion moved on to metabolomics – measuring a single metabolite will not give an answer but if we have lots of data and metabolites we may have more. It is, however, difficult to put metabolomics and biomonitoring together. Most of the time we do not have metabolite data, what is the threshold in the general population and the difference between this and someone who is occupationally exposed?

The main issues with metabolomics relate to costs and amount of data; however it was considered that this science should be taken more into consideration. Currently there still are difficulties in interpreting one metabolite and one situation therefore real issues exist in interpretation with metabolomics. Metabolomics can have too much sensitivity, and there are still issues with possible contamination from analytical and sampling procedures.

Communication will be the challenge. P4 medicine (predictive, participatory, preventative, personalised) is related to metabolomics, chemicals that proceed over disease. Wireless biosensor movement, real-time longitudinal monitoring through mobile phones is included in this integrated approach to exposure and health. Luxemburg has been persuaded to adopt P4 approach, focusing on wellness rather than health care.

## Lack of toxicity data is biggest concern in current RA vs. Exposure misclassification is the biggest concern in RA

The best way to generate data is through the P4 approach. Have a database of metabolomics signatures exposure to disease. This is where modelling will link. Reconstruction of exposure will be the big thing from toxicity data. If you know when concentrations cause toxicity then you can work back.

We need to take into account the 'near field' vs 'far field' approach (cfr John Wambaugh). Near field may be more in need of refined exposure data, far field more in need of better toxicity data.

Signatures are already observed for chronic disease. But databases in which signatures are stored (e.g. from metabonomics) are much needed. However it is not a waste of time to collect exposure data. The stakeholders agreed that there was a need for more toxicity data. Yet, why choose one over the other? It was felt that we have to provide details of general population levels and how this compares. Nevertheless, we still need proper exposure data/assessment as that is what will base actions and eventual risk management measures. Toxicity in the 21st century is generating data to help with this. But the question arose on whether we should keep looking for early (uncertain) markers, or rather for true health outcomes upon which to base reverse dosimetry approaches.

## What is the difference between occupational and environmental or consumer exposure priorities? Should you have the same model for both?

The model itself can be the same, it is how you feed into the various parameters that will differ. It is anticipated that modellers would make different assumptions to take account of route.

Exposure scenarios are important – toxicity endpoints acute vs. chronic which relate in part to exposure scenario; therefore the input data are important. Normal population can be a lot more sensitive than workers and this should be considered, since the general population is much more diverse than the worker population. Furthermore, occupational exposure often works with clear limit values (above this number, there is a problem), environmental exposure does not have these thresholds.

Building in different exposure scenarios is very important; which is a typical behavioural/exposure pattern? This is easier for occupational exposure, much more difficult for environmental exposure

The POPGEN database is freely available. Used to generate population-based cohort. It is in INTEGRA already. Time from previous urine void is a very important parameter to consider for proper interpretation of human biomonitoring values.

## Final thoughts

A model is not the alpha and omega of risk assessment, but it helps to identify methodological and knowledge gaps. Models do not provide the final answers, but they provide insight. Modellers challenge themselves constantly in trying to approach reality as closely as possible, but still are aware of the limitations of the models. Non-modellers take the data without these concerns.

A stoplight approach was proposed, in which (if available) clearly defined action levels are included in different tiers of the model. If a chemical is in the "green" area of a very simple tier 0 model, no need for further refinement; if it's in the orange or red zone, proceed to more complicated tier 1 and tier 2 models. Like this, the model can be made up out of building blocks. Start very simple, and add complexity when needed. Also, the output needs to be easily interpretable (see e.g. the outcome of the CEFIC-project by G. Loizou)

Participants were advised that a second workshop will be held next year when the model and user interface will be presented and feedback requested.

## Conclusions

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.