Application of an integrated approach to evaluate health risks for toxic chemicals by linking multimedia environmental and PBPK models

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1. Introduction

The paradigm of health risk assessment may consist of two main pillars, i.e., the exposure and dose-response assessments. Human exposure to chemicals via multiple pathways can be estimated by environmental multimedia models, which calculate the distribution of chemicals in the component media. Combined with the information about human behaviours such as dietary habits, the multimedia models can provide an estimation of the daily chemical intake via inhalation or ingestion by humans. Physiologically based pharmacokinetic (PBPK) models are used to estimate the body burden of toxic chemicals throughout the entire human lifespan, integrating the evolution of the physiology and anatomy from childhood to advanced aged (Beaudouin et al. 2010).

A main objective of the European project called 2-FUN is to improve the approaches currently used in exposure and dose-response assessments. According to the aim of that project, an environmental multimedia model and a generic PBPK model are coupled as an integrated tool (2-FUN tool) and built up on a platform system, Ecolego®. This study aims at demonstrating the first application of the integrated tool to perform the full-chain risk assessment of a chemical for human health, considering multiple exposure pathways of chemical via inhalation of out-door air, and ingestion of water and foods. For this application of the tool, a case study was designed based on the information obtained from a region situated on the Seine river watershed, downstream of the Paris megacity and Benzo(a)pyrene (B(a)P) was selected as a target chemical substance. This study focuses especially on the propagation of uncertainty and inter-individual variability along the modelling chain. A probabilistic simulation was then performed to identify the input parameters and exposure pathways sensitive to specified model outputs.

2. Materials and methods

The 2-FUN tool consists of six compartments; air, freshwater, soil/groundwater, plant (root, potato, leaf, grain, and fruit) compartments, which constitute a multimedia environmental model, and human compartment, which is corresponding to a generic PBPK model. The multimedia model calculates the daily B(a)P exposure via inhalation and ingestion to humans. The calculated exposure outputs are automatically used as inputs in a PBPK model to estimate final model outputs.

In the designed case study, there are two model inputs associated with B(a)P levels; one is B(a)P concentration in river water at the upstream zone, and the other is B(a)P concentration in the air flow entering the target region. The long-term time series of B(a)P concentrations in the upstream of zone (1993-2008) were obtained from the database made by the Seine-Normandy Water Management Agency (SNWMA). The long-term time series of B(a)P concentrations in the air flow was made up based on the information in Quéguiner et al. (2010). A simulation by the 2-FUN tool was performed over the period corresponding to that for these model inputs (1993-2008).

The model outputs of interest in the case study are the concentration of B(a)P in the liver and lungs, and the total quantity of metabolites formed in liver and lungs. To perform a global sensitivity analysis and an uncertainty analysis for the defined model outputs, only the key parameters potentially influential to the model outputs were in advance selected and assigned their corresponding probability density functions (PDFs).

3. Results and discussion

The magnitude of sensitivity is shown by relative sensitivity index. Figure 1 presents the average index value over the simulation period for each parameter. The result for each output is as follows:

- *Concentration of B(a)P in liver:* The most influential parameter is maximal velocity for metabolism in liver ($Vmax_{liver}$), followed by growth rate of leaf ($K_{g, leaf}$), and maximal velocity for metabolism in lungs ($Vmax_{lung}$).
- *Concentration of B(a)P in lungs:* Maximal velocity for metabolism in liver ($Vmax_{liver}$), followed by growth rate of leaf ($K_{g, leaf}$), and Michaelis constant for metabolism in lungs (Km_{lung}).
- *Metabolites in liver:* Partition coefficient between air and water in leaf ($K_{AW,leaf}$), followed by Octanol-water partition coefficient in grain ($K_{OW,graiin}$) and growth rate of leaf ($K_{g, leaf}$).
- *Metabolites in lungs:* Maximal velocity for metabolism in lungs ($Vmax_{lung}$), followed by Michaelis constant for metabolism in lungs (Km_{lung}) and liver (Km_{liver})

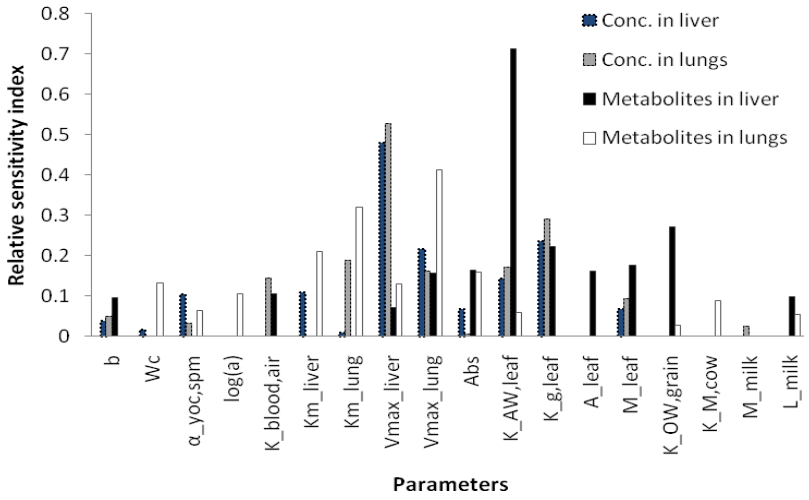

Figure 1: A global sensitivity analysis for specified model outputs

These results indicate that the parameters used in human and leaf compartments have relatively high sensitivity to all the specified model outputs.

4. Conclusions

The model outputs of 2-FUN tool are not explicitly able to indicate health risks (e.g., risks of cancers in liver and lungs) at this stage of model development. Nevertheless, it can be concluded that 2-FUN tool has the potential applicability for health risk assessment, taking into account multiple exposure pathways via inhalation and ingestion. For the further development of the 2-FUN tool, the following points should be considered in future studies:

- To compare simulated results (internal B(a)P concentrations and accumulated quantities of metabolites in the target organs) with the corresponding bio-monitoring data, and to evaluate the model performance
- To incorporate dose-response functions into the 2-FUN tool to facilitate the evaluation of potential risks of human disease occurrences
- To add dermal intake as a main exposure pathway

5. References

[1] Beaudouin R, Micallef S, Brochot C. 2010. A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. *Regul Toxicol Pharm* 57: 103-116.

[2] Quéguiner S, Genon LM, Roustan Y, Ciffroy P. 2010. Contribution of atmospheric emissions to the contamination of leaf vegetables by persistent organic pollutants (POPs): Application to Southeastern France. *Atmos Environ* 44: 958-967.

Acknowledgement – This work has been carried out in the framework of 2-FUN (Full-chain and UNcertainty Approaches for Assessing Health Risks in FUture ENvironmental Scenarios) project [FP6, Contract N: 036976].