An exposure reconstruction model for environmental and consumer product chemicals: Application on Bisphenol A

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The combination of human Physiologically Based BiokineticKinetic (PBBK) models and biomonitoring aiming to the evaluation of environmental exposure of humans to chemicals is an ongoing research field known as exposure reconstruction or reverse dosimetry. The major benefit of this retrospective interpretation is that it can be used to quantify both aggregate and cumulative exposure. Uncertainties of the method rely on the validity of the PBBK models, the analytical error and the fir for purpose of the biomonitoring data as well as to the employed exposure reconstruction algorithms.

Assimilation of human biomonitoring data and their translation into intake distribution amounts to a computational inversion problem, where the objective is to identify the specific input distributions that best explain the observed outputs while minimizing the residual error. Inputs involve spatial and temporal information on micro-environmental media concentrations of xenobiotics and corresponding information on human activities, food intake patterns or consumer product use that result in intakes; outputs are the observed biomarkers. The error metric can be defined in terms of population variation (the latter has to be lower than the intra-individual variation, which may be associated to measurement or other random error source). At the individual level, the PBBK model is combined with multimedia models and survey questionnaires to identify exposure sources, used as ancillary information, aiming to predict exposure magnitude and eventually the timing of exposure events.

In this study an exposure reconstruction model was coupled with a generic PBBK model aiming at reconstructing exposure from biomonitoring data from industrial chemicals.

The developed exposure reconstruction framework consists of 3 basic steps:

- At first the prior parameter distribution, the joint probability distribution, the population model and the determination of the measurement model have to be specified.
- At the next step exposure is calculated using MCMC simulation considering the observed biomonitoring data.
- Finally, the evaluation of the results is realized using MC simulation, with emphasis to the comparison of prior and posterior distribution as well as parameter independence.

MCMC simulation refers to a class of iterative simulations in which the random variables of interest are drawn from a sequence, or chain, of distributions that eventually converge to a stable posterior distribution. Moreover, Differential Evolution (DE) and MCMC algorithms have been combined to this problem for the first time. Differential Evolution Markov Chain is a population MCMC algorithm, in which multiple chains run in parallel. In fact DE is a simple genetic algorithm for numerical optimization in real parameter spaces. As a result, this combined computational framework speeds up the calculation and convergence, even for nearly collinear parameters and multimodal densities. The analysis of exposure reconstruction problems is based on the MCMC

and DEMC technique and it has been carried out according to the following steps: The external exposure are connected (through oral, skin and inhalation routes of exposure) to the PBBK model. Then, the probability model is specified according the prior parameter distributions as well as the calculated and/or fixed distribution of the pharmacokinetic model. The PBBK model has been combined with the Bayesian MCMC and DEMC techniques in order to simulate and calculate the expected value of the exposure.

The generic model was applied for the assessment of a highly controversial industrial chemical with widespread applicability in consumer goods, namely bisphenol-A (BPA). Exposure scenarios were built based on an extensive literature review of BPA exposure data and the generic PBBK model was properly parameterized. BPA is considered to be rapidly conjugated into BPA glucuronide (BPA-Glu), resulting in rapid elimination from the human body due to the water solubility of this metabolite.

Exposure to BPA was reconstructed based on real-life HBM European data. Average urinary glucuronidated bisphenol-A (BPA-Glu) was 2.8 μ g/L across Europe, covering different age groups, using an average urine BPA-Glu equal to 2.8 μg/L. In particular the algorithm has been tested under the assumption that the average amount of 2.8 μg/L BPA-Glu to human' s urine is the results of an ordinary adult dietary schedule that includes 3 different meals: i) breakfast at 7:00 am (dose 1), ii) lunch at 2:00 pm (dose 2) and iii) dinner at 7:00 pm (dose 3). The results of the exposure reconstruction algorithms after 1000 iterations converge to the available biomonitoring data. All the prior distribution have been moved through to the direction of the actual exposure dose. The results indicated that the overall daily intake is very low, approximately 1 μg/kg_bw/d, which is far below the Tolerable Daily Intake (TDI) of 50 μg/kg_bw/d proposed by the European Food Safety Authority (EFSA). Comparing the computation needs of the algorithms, the DEMC is 3 to 4 time slower than MCMC but the predictions have better approach to the actual value, when the algorism were tested again synthetic data for validation purposes. The high frequency exposure interval representing the real life exposure scenario of this study increases the computation needs. The need for better awareness of biomarker levels is obvious in case of the exposure to chemical substances and more when the substances are rapidly metabolized. The algorithm of DEMC is used for first time in exposure reconstruction models providing clear benefits in terms of biomonitoring data assimilation, however, additional optimization of the code will result in smaller computational time. A generic and reliable generic (covering a large chemical space) exposure reconstruction scheme, could be a very useful tool for modern risk assessment of chemicals, utilizing the large amount of existing human biomonitoring data.