ADVANCING CHEMICAL RISK ASSESSMENT THROUGH HUMAN PHYSIOLOGY-BASED BIOCHEMICAL PROCESS MODELING

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ABSTRACT

Physiology Based BioKinetic (PBBK) models are of increased interest in modern risk assessment, providing quantitative information regarding the absorption, metabolism, distribution and excretion (ADME). They focus on the estimation of the effective dose at target sites, aiming at the identification of xenobiotic levels, able to result in perturbations to biological pathway, potentially associated with adverse outcomes. One of the main applications of internal dosimetry is the integration of exposure and HBM data. More in detail, internal dosimetry aims at i) deriving the time course of the toxicants in human tissues, with a particular focus on susceptible developmental stages; ii) providing a comprehensive interpretation of the HBM data related to the cohorts, for quantifying individual exposome; and iii) deriving Biologically Effective Dose (BED) values for associating them to adverse outcomes. The need for developing generic PBBK models is of great importance in modern risk assessment, especially for compounds where toxicokinetics play a particular role in their overall adverse effects in humans. Among these compounds, Bisphenol A (BPA), is a commonly used plasticizer of increased scientific and regulatory interest. BPA is used in the manufacture of polycarbonate plastics and epoxy resins, as protective coatings on food containers, as well as in dentistry, thermal paper and polyvinyl chloride industries. Based on the above, the current study aims at the development of a lifetime PBBK model that covers a large chemical space, coupled with a framework for human biomonitoring (HBM) data assimilation. The methodology developed herein was demonstrated in the case of bisphenol A (BPA), where exposure analysis was based on European HBM data. For the assessment of BPA exposure, HBM data were collected from the available literature. Urinary BPA concentrations reflect differences in consumer exposure related to food packaging material (canned food, milk formula, use of plastic baby bottles). In the most recent studies, urinary BPA (in the form of the glucuronidated metabolite) measured levels are about 2 μg/L. Based on our exposure reconstruction calculations, it was found that current exposure levels in Europe are below the temporary Tolerable Daily Intake (t-TDI) of 4 μg/kg_bw/d proposed by the European Food Safety Authority (EFSA). Among the investigated population groups, higher mean intake levels were estimated for children. On the other hand, the similar maximum exposure estimates (close to 0.8 μg/kg_bw/d) for all age groups, indicates that significant exposure sources still occur for both adults and children. Taking into account age-dependent bioavailability differences, internal exposure was estimated and compared with the biologically effective dose (BED) resulting from translating the EFSA temporary total daily intake (t-TDI) into equivalent internal dose and an alternative internal exposure reference value namely biological pathway altering dose (BPAD).On the other hand, these exposure levels might result in a daily AUC similar to the one derived by t-TDI, depending on the presence of alleles associated to slower metabolism of the individuals. Our forthcoming work will focus on BPA substitutes, BPS and BPF, the toxicity of which is yet to be determined due to uncertainties on their biokinetic and biochemical behavior. The multi-faceted method presented herein, provides more accurate daily intake estimates compared to the method based on urinary concentrations mass balance, since the use of physiology based biokinetic modeling allows the comprehensive description of exposure and elimination time dynamics. This highlights the importance for using PBBK modelling based exposure reconstruction schemes for rapidly metabolized and excreted compounds such as BPA. In addition, the use of such a refined exposure metric, showed that environmentally relevant exposure levels are below the concentrations associated with the activation of biological pathways relevant to toxicity based on High Throughput Screening (HTS) *in vitro* studies.