An integrated tool for risk assessment for industrial chemicals – the case of bisphenol A

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Human exposure needs to be reckoned based on media concentrations and contact duration while exposure mechanisms (pathways and relevant routes) need to be identified to properly assess total exposure to endocrine disruptors. Based on the temporal variation of exposure and accounting for the contribution of different exposure routes the internal dose in target tissue(s) can be calculated. The distribution of exposure to the wider population or specific susceptible groups (e.g. infants) has to be computed and apportioned to each source or possible exposure patterns when biological indices of exposure (biomarkers) are measured (reverse modelling/exposure reconstruction). Finally, available biomonitoring data can be compared with regulatory thresholds using the concept of biomonitoring equivalent to the reference dose, or even with an actual internal dosimetry related reference value derived by biomonitoring surveys. The INTEGRA project (funded by CEFIC-LRI) provides the computational platform that integrates environmental fate, exposure and internal dose dynamically in time aiming to advance risk assessment from xa xa the "exposure based" risk assessment era.

Beyond the multimedia environmental and aggregate exposure modelling fremework, a major methodological component of INTEGRA is the incorporated generic Physiology Based BioKinetic (PBBK) model. The model is designed to describe as much as possible the actual ADME processes occurring in human body, so as to be easily applicable for a broad variety of chemicals under proper parameterization. The model includes the parent compound and its three main metabolites. For each compound/metabolite all major organs is included and the link among the compounds and the metabolites is through the metabolizing tissues. This is mainly the liver, but also other sites of metabolism might be considered based on the presence or not of the enzymes involved in the metabolism of the compound of interest. Both phase I and phase II metabolism are described mathematically. Both membrane and blood flow limited processes are included. In order to capture the in-utero exposure, the model is also replicated in order to describe the functional interaction of the mother and the developing fetus through the placenta. The anthropometric parameters of the models are age dependent covering the whole lifespan from the moment of conception, so as to provide a lifetime internal dose assessment.

The PBBK model is geared with reverse modeling algorithms in order to reconstruct exposure from human biomonitoring (HBM) data. A tiered approach is followed as a function of data availability (periodicity and size of sampling, specimen type) and requirements of the exposure reconstruction analysis (temporal analysis of exposure, contribution from different routes), ranging from Exposure Conversion Factors (ECFs), up to Markov Chain Monte Carlo analysis. Probabilistic techniques are used to validate the exposure outcome on the basis of actual environmental and population biomonitoring data. 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.

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.

In order to associate the risk of the several exposure scenarios based on the Biologically Effective Dose (BED) derived by the PBBK model, two different exposure metrics were used:
- The Tolerable Daily Intake (TDI) of 50 μg/kg_bw/d proposed by the European Food Safety Authority, was translated into internal exposure, found to correspond to a concentration of 0.16 μg/L of free plasma BPA.
- *In vitro*, the ToxCast assays provided six ER agonist or binding AC50 values for BPA, ranging from 0.6 to 1.7 μM. To calculate a conservative Biological Pathway Altering Dose (BPAD), the lowest ToxCast AC50 was selected (0.64 μM for Attagene Factorial cis ERE assay). This estimated concentration (145 μg/l), is 3 orders of magnitude higher than the equivalent derived from the EFSA TDI (0.16 μg/l).

For the majority of scenarios, the estimated internal dose was close to 0.002 μg/L and only in the case of bottle fed infants, internal exposure concentrations were up to 0.023 μg/L. This is partially explained by the neonates immaturity of the detoxification pathway, resulting to higher internal doses for the same bodyweight normalized dose compared to children older than 1 year old or adults. The biologically effective dose of the developing fetus during gestation is highly linked to the one in maternal blood. According to our model and based on a conservative exposure scenario for the mother (e.g. 5 μg/kg_bw/d), free plasma BPA in maternal blood. In addition, exposure to BPA was reconstructed based on real-life HBM data. Average urine BPA-Glu was 2.8 μg/L across Europe, covering different age groups, using an average urine BPA-Glu equal to 2.8 μg/L. The results indicated that the overall daily intake is below 1 μg/kg_bw/d and the estimated internal dose was close to 0.002 μg/l, far below any internal dose derived reference value, corresponding to the lower estimates of the already considered exposure scenarios. The only scenario of concern was the one related to premature neonates hosted in intensive care units. However, the risk characterization ratio depends on the threshold considered. If *in vitro* data are used, all exposure scenarios are considered as safe.

Assessment of real life exposure scenarios can be estimated following either a bottom-up (starting from exposure estimates), or a top-down (starting from biomonitoring data). In any case, the assessment is efficiently refined if internal dose metrics are used as reference doses for risk characterization. The latter can be derived by extrapolating from *in vivo* or *in vitro* results, taking stock of the wealth of data rapidly produced by modern high-throughput platorms.