

In emerging approaches - Handbook 2021 Workshop

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Cumulative Risk Assessment Approach for Mixtures

Pletz *et al.*, (2020) investigated the suitability and limitations of generic PBPK models (IndusChemFate (ICF) tool [Cefic website](#) and High-Throughput Toxicokinetics (Httk) package [US EPA website](#)) in deriving biomonitoring equivalents for phenols (bisphenol A, Triclosan and benzophenone-3), phthalates (di-*n*-butyl phthalate and butylbenzyl phthalate) and parabens (methyl paraben, ethyl paraben, *n*-Propyl paraben, *n*-Butyl paraben) with a view to facilitating the use of human biomonitoring (HBM) data in the assessment of chemical mixtures at a screening level (i.e. establishing safe levels in urine or blood against which measure HBM values can be compared).

In brief, the methodology consisted of seven steps:

- i). The selection of HBM data - Danish children and on Norwegian mothers and children;
- ii). PBPK model selection - ICF and Httk package;
- iii). Selection of chemicals to simulate including a literature search for health-based guidance values and selection of physiological parameters in the model;
- iv). Forward dosimetry;
- v). Evaluation of modelling results;
- vi). Application in a case study for a single substance risk assessment and;
- vii). Application in a case study for mixture risk assessment with outputs from the Httk analysis.

The authors noted both advantages and limitations of both PBPK models. For ICF, the main advantage was that the model included features for inclusion of metabolism, however, it required a substantial number of input parameters which were not readily available within the literature. For Httk, the advantage was that it had an in-built library of relevant parameters covering many chemicals and thus was considered to be more user- friendly, however, in the version tested (version 1.8), metabolism was only addressed via intrinsic clearance and thus predictions of metabolite concentrations could not be included.

It was concluded that the application of PBPK models provided a greater understanding and interpretation of HBM data. Although, the establishment of safety thresholds in urine for the compounds tested was difficult and complex. Model refinement was also recommended to reduce uncertainties (regarding metabolite concentrations) and improve predictions.