Health risk assessment of chemical mixtures is frequently conducted on the basis of exposure and toxicity information for individual components. Routine application of physiologically-based toxicokinetic (PBTK) models in mixture risk assessment is limited by the availability of the appropriate PBTK models for chemical mixtures, the number of parameters that need to be specified, and the complexity of applying these PBTK models. Case studies addressing these limitations are presented via the application of a previously developed multi-chemical PBTK modeling framework. In the first case study, a PBTK model for a mixture of polychlorinated biphenyls (PCBs) in the rat was reformulated to incorporate a hierarchical treatment of population parameters, and a proposed model for toxic interactions. Assumptions based on the lipophilicity of PCBs significantly reduced the number of model parameters. These parameters were then estimated through the application of a Bayesian Markov Chain Monte Carlo (MCMC) analysis through model-data fusion. In the second case study, further improvements in the performance and applicability of mixture PBTK models are presented through efficient algorithms that identically reproduce the steady-state outputs of PBTK models. Since human exposures to environmental chemicals frequently lead to steady-state conditions, it is pragmatic to develop a tool that provides the steady-state solutions of full PBTK models of mixtures by accounting for the nature and magnitude of interactions. A steady-state solution was developed for computing dose metrics (i.e., blood concentration and metabolism rate) during mixture exposures and applied for computing interaction-based hazard index for mixtures of organics (toluene, xylene, ethylbenzene, carbon tetrachloride and tetrachloroethylene). The presentation focuses on the application of these techniques based on sound exposure biology by risk assessors.

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