Integrating Population Enzyme Variability Into Physiologically-Based Kinetic Models of Parent Chemicals and Metabolites

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Chemicals that enter the body are broken down into metabolites by enzymatic activity from a range of metabolic pathways. Rates of metabolism can vary across human populations due to inter-individual genetic variability, making some populations potentially slower in metabolism and more sensitive to effects from parent chemicals or their metabolites. Risk assessors apply physiologically-based kinetic (PB-K) models to depict the dynamics of tissue concentrations for both parent chemicals and metabolites, but technical and data limitations often make it difficult to apply these models to characterize the effects of enzymatic pathway-related variability within populations. We developed a generalized workflow for incorporating pathway-related variability for select Phase I cytochrome P450 (CYP) and Phase II UGT enzymes across human populations into PB-K models. The elements of the workflow include metabolite structures generated using SimulationsPlus ADMET Predictor®, PB-K models from the U.S. Environmental Protection Agency's httk R package, estimates of enzyme variability from EFSA literature reports, and parameter predictions from OPERA (v2.8). Data on inter-individual genetic variability in enzyme activities are integrated into httk models by applying pathway-related variability distributions to intrinsic clearance parameters of parent chemicals. Parent chemical dynamics are simulated following an initial exposure and the amount of parent chemical metabolized is scaled by the percent yield to provide intravenous input time series for metabolite models. OPERA physiochemical and ADME property predictions are used to parameterize the httk models and simulate parent and metabolite concentrations over time. The httk models are then reparametrized using Monte Carlo sampling of enzymatic variability in intrinsic clearance, generating a range of concentrations that are representative of potential population variability. To demonstrate the dynamics of the workflow, we applied it to a case study of 10 parent chemicals and their metabolites. One such chemical is morpholine, which has 4 predicted metabolites from one round of CYP3A4 and CYP2D6 metabolism. Following a single oral bolus of morpholine, the PB-K workflow output showed the highest percent yield metabolite (42%) had the highest potential tissue and plasma concentration, with a maximum plasma concentration of up to 0.1331 mg/L. The lowest percent yield metabolite (11%) had the lowest potential tissue and plasma concentration with a plasma concentration of up to 0.0501 mg/L. However, the differences in concentration were relatively small, as the metabolites' unique clearance rates likely offset the varying metabolite yields. This workflow will eventually be expanded to approximately 800k chemicals in the SimulationsPlus ADMET Predictor database with multiple rounds of metabolism considered. Our approach supports hazard and risk characterization for sensitive subgroups by identifying the maximum tissue concentrations for potentially toxic chemicals in a population. Furthermore, the workflow can be used to simulate chemical concentrations in select subpopulations by modifying enzyme inputs to represent a demographic subset. This project was funded with federal funds from NIEHS, NIH under Contract No. HHSN273201500010C.

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