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 genetic variability, making some populations potentially more sensitive to effects from parent chemicals or 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 use these models to characterize the effects of pathway-related variability within populations. We developed a generalized workflow for incorporating pathway-related variability for a range of enzymes across human populations into PB-K models. The elements of the workflow include metabolite predictions generated using SimulationsPlus' ADMET Predictor®, PB-K models from the U.S. Environmental Protection Agency's httk R package, and parameter predictions from the Open Structure-activity/property Relationship App (OPERA v2.8). Data on genetic variability in enzymatic activity were integrated into httk models by applying pathway-related variability distributions to intrinsic clearance parameters of parent chemicals. Parent chemical dynamics were simulated following an oral bolus exposure and the amount of parent chemical metabolized was scaled by percent yield to provide intravenous input time series for metabolite models. Ranges of parent and metabolite concentrations were predicted based on enzymatic variability. This approach supports hazard and risk characterization in sensitive subgroups by identifying the maximum tissue concentrations for potentially toxic chemicals in a population. This project was funded with federal funds from NIEHS, NIH under Contract No. HHSN273201500010C.