Integrating Enzyme Variability Into PB-K Models of Chemicals and Metabolites

V. Hull[1*], D. Hines[2], A. Unnikrishnan[1], A.L. Karmaus[1], D.G. Allen[1], J.L. C.M. Dorne[3], J. Erickson[4], P. Combs[4], S. Ferguson[5], K. Mansouri[6], and N. Kleinstreuer[6]

[1]Inotiv, RTP, NC, United States; [2]RTI International, RTP, NC, United States, [3]European Food Safety Authority (EFSA), Parma, Italy; [4]NIH/NIEHS/DTT/PTB, RTP, NC, United States; [5]NIH/NIEHS/DTT/MTB, RTP, NC, United States;
[6]NIH/NIEHS/DTT/PTB/NICEATM, United States*, RTP, NC, United States*

**Presenting author*

Chemicals that enter the body are metabolized via a number of pathways. These rates of metabolism can vary across human populations due to genetic variability of metabolic enzymes, meaning some populations are more sensitive to effects of parent chemicals or metabolites. Risk assessors apply physiologically based kinetic (PB-K) models to predict the dynamics of tissue concentrations for parent chemicals and their metabolites, but it is difficult to use these models to characterize the effects of enzymatic pathway-related variability. We developed a generalized workflow for incorporating pathway-related variability for select Phase I CYP and Phase II UGT enzymes across human populations into PB-K models. The workflow includes metabolite structures generated using SimulationsPlus ADMET Predictor®, PB-K models from EPA's httk package, estimates of inter-individual enzyme variability from EFSA literature reports, and parameter predictions from OPERA (v2.8). Parent chemical dynamics are simulated following initial exposure and the amount of parent metabolized is scaled by percent yield to provide an intravenous time series for metabolite models. Ranges of parent and metabolite concentrations are estimated by Monte Carlo sampling of enzymatic variability in intrinsic clearance. This presentation will demonstrate the dynamics of the workflow and include a case study of 10 parent chemicals and their metabolites. The workflow provides a characterization of tissue concentration dynamics for potentially toxic chemicals to support estimates of hazard and risk for sensitive subgroups of an exposed population. Results will eventually be accessible through the Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/). This project was funded by NIEHS under Contract No. HHSN273201500010C.