Realistic human variability in high-throughput risk prioritization of environmental chemicals

C. Ring[1,2], W. Setzer[2], R Pearce[2], J. Wambaugh[2]

[1]Oak Ridge Institute for Science and Education Postdoctoral Fellow, [2]United States Environmental Protection Agency, Office of Research and Development, National Center for Computational Toxicology, Research Triangle Park, North Carolina

Abstract: We incorporate realistic human variability into an open-source high-throughput (HT) toxicokinetics (TK) modeling framework for use in a next-generation risk prioritization approach. Risk prioritization involves rapid triage of thousands of environmental chemicals, most which have little or no existing TK data. Chemicals are prioritized based on model estimates of hazard and exposure, to decide which chemicals should be first in line for further study. Hazard may be estimated with *in vitro* HT screening assays, *e.g.*, U.S. EPA's ToxCast program. Bioactive ToxCast concentrations can be extrapolated to doses that produce equivalent concentrations in body tissues using a reverse TK approach in which generic TK models are parameterized with 1) chemical-specific parameters derived from *in vitro* measurements and predicted from chemical structure; and 2) with physiological parameters for a virtual population. Here we draw physiological parameters from realistic estimates of distributions of demographic and anthropometric quantities in the modern U.S. population, based on the most recent CDC NHANES data. A Monte Carlo approach, accounting for the correlation structure in physiological parameters, is used to estimate ToxCast equivalent doses for the most sensitive portion of the population. To quantify risk, ToxCast equivalent doses are compared to estimates of exposure rates based on Bayesian inferences drawn from NHANES urinary analyte biomonitoring data. The inclusion of realistic human variability in the TK modeling framework allows targeted risk prioritization for demographic groups of interest. (This abstract does not necessarily represent U.S. EPA policy.)