# Uncertainty and Variability in High-Throughput Toxicokinetics for Risk Prioritization

John F. Wambaugh[1], Barbara A. Wetmore[2], Derek Angus[3], Chris Strock[3], Maria Bacolod[3], Chantel I. Nicolas[4], Caroline L. Ring[5], Robert G. Pearce[1], R. Woodrow Setzer[1], Russell S. Thomas
1National Center for Computational Toxicology
2National Exposure Research Laboratory
Office of Research and Development
US EPA, Research Triangle Park, NC 27711
3Cyprotex US, LLC, Watertown, MA 02472
4ScitoVation LLC, Research Triangle Park, NC 27709
5ToxStrategies, Inc., Austin, TX 78759

Streamlined approaches that use *in vitro* experimental data to predict chemical toxicokinetics (TK) are increasingly being used to perform risk-based prioritization based upon dosimetric adjustment of high-throughput screening (HTS) data across thousands of chemicals. However, assessments of the impact of uncertainty and variability on these TK values and subsequent predictions are needed to guide data interpretation and provide overall confidence in high-throughput TK (HTTK) approaches. In this study, Bayesian methods were developed to provide chemical-specific uncertainty estimates for two *in vitro* TK parameters: plasma protein binding ($f_{up}$) and intrinsic hepatic clearance ($Cl_{int}$), using chemical-specific experimental measurements derived. Inclusion of experimental measures across three physiologic plasma protein concentrations reduced the uncertainty in the $f_{up}$ estimates. Uncertainty estimation was additionally conducted for predictions of volume of distribution ($V_d$) and steady-state serum concentration ($C_{ss}$). Monte Carlo simulation to propagate both measurement uncertainty and biologic variability into the predicted $C_{ss}$ values revealed that for most chemicals, variability contributed more than uncertainty to $C_{ss}$ estimations of the 95th percentile. Risk-based prioritization of chemicals based upon high throughput exposure estimates and dosimetric adjustment of ToxCast HTS data using Bayesian-derived $C_{ss}$ estimates incorporating uncertainty and/or variability demonstrated that prioritization would change for a few chemicals when uncertainty is included. Incorporation of these methods provides a timely risk-based prioritization strategy that considers the relationship between in vitro bioactivities and exposures, overlaid with a metric for TK prediction certainties. *This abstract does not necessarily reflect U.S. EPA policy.*