# The Use of Bayesian Methods for Uncertainty Analysis and Evaluation of Biological Hypotheses in PBPK Models

J.L. Davis[1], R. Tornero-Velez[2], J.F. Wambaugh[1], R.W. Setzer[1]

[1]National Center for Computational Toxicology, [2]National Exposure Research Laboratory, US EPA, Research Triangle Park, NC

Physiologically based pharmacokinetic (PBPK) models are compartmental models that describe the uptake and distribution of drugs and chemicals throughout the body. They can be structured so that model parameters (i.e., physiological and chemical-specific) reflect biological characteristics. Bayesian methods can be used to combine prior information derived from the literature (e.g., mean values, chemical structure, and *in vitro* data) in the form of probability distributions on PBPK model parameters with new information from *in vivo* data to determine parameter estimates and model uncertainties. These methods can also be used to evaluate and refine biological modeling assumptions underlying PBPK models. Using a PBPK model developed for permethrin in rats, we combine prior information from the literature on several of the PBPK model parameters (e.g., blood flows, partition coefficients, metabolic rate constants) with measured concentrations of both the *cis*- and *trans*- isomers of permethrin in various tissues for uncertainty analysis and model evaluation. We evaluate biological assumptions used to describe partition coefficients via Schmitt's predictive model (2008) by comparing the model fits of two different permethrin PBPK models. In the first version of the model, partitioning is characterized by the explicit use of standard tissue-specific partition coefficients as PBPK model parameters. In version two of the permethrin PBPK model, we use Schmitt's 2008 model based on tissue composition, solubilities, and binding properties to compute the partition coefficients for each tissue or compartment within the permethrin PBPK model. We illustrate how Bayesian methods provide a useful statistical framework in which to determine how well the underlying biological assumptions used to model partitioning describe the distribution kinetics of permethrin. *This abstract does not necessarily reflect U.S. EPA policy.*