Quantifying uncertainty in Bayesian calibrated animal-to-human PBPK models with informative prior distributions

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Understanding and quantifying the uncertainty of model parameters and predictions has gained more interest in recent years with the increased use of computational models in chemical risk assessment. Fully characterizing the uncertainty in risk metrics derived from linked quantitative models describing exposure, internal dose, and biological effects poses a significant challenge for the risk assessment community. We are developing computationally efficient and statistically valid methodologies to provide more accurate assessments of uncertainty in risk predictions. In the discussion, we focus on characterizing the uncertainty in physiologically-based pharmacokinetic (PBPK) model parameters and predictions. PBPK models, compartmental models that describe the uptake and disposition of drugs or chemicals throughout the body, can be structured so that model parameters (both physiological and chemical-specific) reflect biological characteristics. Due to limited human pharmacokinetics data for model development and validation, animal models are often parameterized in such a manner that allows extrapolation of PBPK models to humans, resulting in a source of uncertainty that must be assessed. Additionally, uncertainty in PBPK model parameters must also be accounted for even when there is little or no *in vivo* data available for assigning parameter values. In the absence of data, parameter estimates as well as parameter and model uncertainties can be derived from *prior knowledge*, based on chemical structure and information from *in vitro* assays. Bayesian methods can then be used to combine prior information with new information from data to determine parameter estimates and uncertainties. The process of calibrating a PBPK model with Bayesian techniques, using Markov Chain Monte Carlo (MCMC) methods, can require significant computational effort (weeks or months) because of the number of steps required for chains to achieve convergence. In this presentation, we address issues related to parameter estimation, uncertainty quantification, and computational inefficiency of Bayesian PBPK model calibrations. We present some approaches that can be used to develop *informative* priors for chemical-specific PBPK parameters by comparing data sets of measured values with predicted values from computational or *in vitro* methods. Using these approaches, we develop priors for use in a hierarchical Bayesian analysis of a rat permethrin PBPK model. We also discuss how computational runtimes can be decreased via parallelization of MCMC methods. Preliminary results of the Bayesian parameter estimation for permethrin demonstrate the feasibility of these approaches. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*