A General Approach for Specifying Informative Prior Distributions for PBPK Model Parameters

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Characterization of uncertainty in model predictions is receiving more interest as more models are being used in applications that are critical to human health. For models in which parameters reflect biological characteristics, it is often possible to provide estimates of parameters along with uncertainties even in the absence of experimental results against which to compare predictions. Thus, uncertainties for model predictions can be derived from such parameter uncertainty even when there are little or no *in vivo* data available. When appropriate data do exist, such *prior information* (or priors) can be incorporated into Bayesian statistical methods for parameter estimation. Informative priors are often used for physiological parameters in PBPK models to indicate how well-known these parameters are. However, chemical-specific parameters are often assigned vague or weakly informative priors due to much greater uncertainty in parameter values. We describe some approaches that can be used to specify more informative priors for chemical-specific parameters based on information obtained from computational predictors, such as QSAR models, *in vitro* assays, and data sets of measured parameters. In the approaches discussed here, predictions made by computational predictors or *in vitro* assays are compared to experimentally determined chemical-specific values for a selection of chemicals. Standard statistical methods (e.g., linear regression) are used to determine the (bias-adjusted) mean and variance, or coefficient of variation (CV), for the priors quantifying parameter uncertainty. CVs of 50 - 70% computed for various partition coefficients (PCs) with data from an in-depth literature survey demonstrate the validity of these approaches. These methods are also illustrated in an example evaluating the contribution of the uncertainty in PCs to overall PBPK model uncertainty. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*