Integrating parameter uncertainty in PBPK modeling

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Physiologically based pharmacokinetic (PBPK) models combine physiological and chemical-specific parameters to simulate forward and reverse dosimetry, and thus are useful for linking internal concentrations with external doses. Chemical-specific experimental parameter data are needed to run these simulations. When these data are unavailable, quantitative structure-activity relationship (QSAR) models can be used to generate parameter predictions to fill these data gaps. However, the accuracy of QSAR parameter predictions depends on the resemblance of a target chemical to the training set of the model, among other parameters. Understanding how the uncertainty associated with this accuracy affects PBPK model output is essential for interpreting results. We evaluated how QSAR output ranges based on nearest neighbor analysis informs uncertainty in PBPK model predictions. Specifically, parameter value combinations were systematically evaluated based on the full range of parameter values for intrinsic clearance, fraction unbound in plasma, pKa, Henry's law constant, and octanol:water partition coefficient (logP) using the oral gavage and inhalation PBPK models from the U.S. Environmental Protection Agency's httk package. The parameters that influence the maximal and minimal values of response variables were then identified. In this presentation, we will demonstrate how the QSAR-based uncertainty ranges of PBPK model outputs can affect tissue concentration and area-under-the-curve ranges generated by forward dosimetry, and margin of exposure assessments informed by in vitro to in vivo extrapolation.
This project was funded by the National Institute of Environmental Health Sciences, National Institutes of Health, under Contract No. HHSN273201500010C.