Physiologically Based Pharmacokinetic (PBPK) Modeling Approach to Quantify Chemical Distribution in Brain and Adipose Compartments

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Physiologically based pharmacokinetic (PBPK) modeling can be applied to high-throughput applications to facilitate decision-making in drug discovery and risk assessment. However, high-throughput pharmacokinetic modeling is limited to those compartments included within the model, with brain and adipose compartments often lacking due to difficulties in calculating chemical distribution. For the brain, this is complicated by the presence of the blood-brain barrier (BBB), which limits chemical transport and partitioning into the brain. Adipose tissue is particularly complex as it acts both as a storage compartment for lipophilic chemicals and a source of continuous internal exposure as the chemical is subsequently released over time. Estimation of brain and adipose tissue concentrations are, however, important in assessments of neurotoxicity and long-term exposures to persistent chemicals. To address these challenges, we have added brain and adipose tissue compartments to the base PBPK model from the U.S. Environmental Protection Agency's httk R package (v2.2.2). The model workflow was executed in multiple stages including design of model structure, collection of model parameters, model development, curation of validation data, and model evaluation. For the brain compartment, the BBB permeability calculation utilized measured permeability values via transwell assays as well as predictions from a model built with collected measured results. The concentration-time profiles generated by the model overlapped for several tested scenarios including comparisons with experimental data and alternate PBPK model predictions in both brain and adipose compartments. As an example, the Cmax values predicted by the model for brain and adipose tissues were within 2-fold of the experimental data measurements for both hydrophilic chemicals like acetaminophen (predicted Cmax = 54.01, observed Cmax = 74.03) and hydrophobic chemicals like benzo(a)pyrene (predicted Cmax = 11.21, observed Cmax = 9.59). Similarly, the brain Cmax values predicted by the model fell within 10-fold of values predicted by the commercial GastroPlus PBPK model for 92 chemicals with potential developmental neurotoxicity. This alignment between the httk-based brain-adipose model's predictions and predictions from both commercial models and experimental data signifies the robustness of the model and its potential applicability for both drug development and chemical risk assessment.
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