Expanding PBPK Modeling to Predict Chemical Distribution in Brain and Adipose Tissues

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To facilitate decision making in drug discovery and risk assessment, physiologically based pharmacokinetic (PBPK) modeling is used for high-throughput applications. Most existing open-source PBPK models predict chemical concentrations in major body compartments such as liver, kidney, and gut. However, organ-specific toxicological effects require specialized models. For example, models are needed to facilitate neurotoxicity evaluations by predicting chemical distribution to the brain, which has complex structural features and the potential for significant adverse effects. Incorporating the blood-brain barrier in a PBPK model and evaluating whether a chemical can cross this barrier is an important first step in assessing the potential neurotoxicity of the chemical. Another limitation of existing open-source PBPK models is that they often do not include an adipose tissue compartment. Adipose tissue plays a critical role in toxicokinetics by acting as a storage compartment for lipophilic chemicals and a source of continuous internal exposure as the chemical is released. In this study, we added brain and adipose tissue compartments to the existing generic PBPK model from the httk R package (v2.2.2), developed by the U.S. Environmental Protection Agency, to better estimate chemical concentrations in these two tissues. The Open (Quantitative) Structure-activity/property Relationship App's (OPERA) lipophilicity predictions provided estimates on the propensity for accumulation of chemicals in adipose tissue. This presentation describes the creation of this new model and its future implementations in the field of toxico- and pharmacokinetics. This project was funded by the NIH NIEHS under Contract No. HHSN273201500010C and by EPA under Contract No. RD840027.