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 approaches are being developed for high-throughput applications. Most existing open-source PBPK models can predict chemical concentrations in major body compartments including blood, liver, kidney, and gut. However, to help assess specific toxicological effects such as neurotoxicity, models need to predict chemical distribution to compartments like the brain that have complex structural features and may be exquisitely sensitive to chemical exposures. In particular, understanding whether a chemical can cross the blood-brain barrier and incorporating that in a PBPK model is important for predicting and accurately assessing its potential neurotoxicity. Additionally, adipose tissue plays a critical role in toxicokinetics by acting as a storage compartment for lipophilic chemicals and a source of continuous internal chronic exposure as the chemical is released. However, this tissue is often not included as a separate compartment in existing PBPK models. Predicting the concentration of chemicals in adipose tissue by leveraging lipophilicity predictions from QSAR models (e.g., OPERA) can provide valuable information on the likelihood of chemical bioaccumulation. This presentation highlights our work to expand existing PBPK models to quantify chemical concentrations in brain and adipose tissues. Case studies will be used to showcase the functionality of these added compartments and explore their potential future implementations in the field of predictive toxicokinetics. This project was funded by NIEHS under Contract No. HHSN273201500010C.