Rapid Prototyping of PBTK Models for Emergency Response

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Determining the tissue concentrations resulting from chemical exposure (*i.e*., toxicokinetics (TK)) is essential in emergency or other situations where time and data are lacking. Generic TK models can be created rapidly using *in vitro* assays and computational approaches to generate parameter values for particular chemicals. In this study, we evaluate strategies for building simple, reasonably accurate generic models. For 443 chemicals with *in vitro* TK data, we compare predictions of tissue concentrations from a generic perfusion-limited PBTK model to one and two compartment models and also examine the consequences of expanding the model with separate richly and poorly perfused tissue compartments and accounting for tissue blood volumes, using the metrics Cmax, steady state concentration, distribution phase duration, and elimination. These results are then used to develop strategies appropriate for different classes of chemicals. The largest difference in the model expansions, due to lumping, is the longer duration of the distribution phase of the model with richly and poorly perfused compartments, still within a factor of 2. A 2-compartment model, parameterized with physiological parameters, closely fit its equivalent PBTK model, and metrics were mostly within a factor of 2. Although tissue lumping decisions can be guided by toxicological concern (e.g., brain), evaluation of 856 chemicals revealed that chemicals readily classified into three groups of low, medium, and high tissue partitioning: hydrophilic acids (mean logP of ~0.7, e.g., aspirin), lipophilic neutrals (mean logP ~3, e.g., PCBs), and lipophilic bases (mean logP ~3, e.g., morphine), respectively. The accuracy of predictions of tissue concentrations varies systematically with tissue across chemicals, with gut and lung concentrations relatively accurately predicted, while the accuracy of adipose and brain concentrations was relatively poor. Finally, we identify those chemical classes where *in silico* models for TK parameters may eliminate the need for *in vitro* measurement. By eliminating the more complicated model elements, our approach is broadly applicable across many classes of chemicals. These prototypes provide simpler models that can be understood, parameterized, and transferred across platforms. *This abstract does not necessarily reflect U.S. EPA policy.*