Evaluation of Pharmacokinetic Assumptions Using a 443 Chemical Library

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With the increasing availability of high-throughput and <I>*in vitro*</I> data for untested chemicals, there is a need for pharmacokinetic (PK) models for <I>*in vitro*</I> to <I>*in vivo*</I> extrapolation (IVIVE). Though some PBPK models have been created for individual compounds using <I>*in vivo*</I> data, we are now able to rapidly parameterize generic PBPK models using <I>*in vitro*</I> data to allow IVIVE for chemicals tested for bioactivity via high-throughput screening. However, these new models are expected to have limited accuracy due to their simplicity and generalization of assumptions. We evaluated the assumptions and performance of a generic PBPK model (R package "httk") parameterized by a library of <I>*in vitro*</I> PK data for 443 chemicals. We evaluate and calibrate Schmitt's method by comparing the predicted volume of distribution (V_d) and tissue partition coefficients to <I>*in vivo*</I> measurements. The partition coefficients are initially over predicted, likely due to overestimation of partitioning into phospholipids in tissues and the lack of lipid partitioning in the <i>in vitro</I> measurements of the fraction unbound in plasma. Correcting for phospholipids and plasma binding improved the predictive ability (R^2 to 0.52 for partition coefficients and 0.32 for V_d). We lacked enough data to evaluate the accuracy of changing the model structure to include tissue blood volumes and/or separate compartments for richly/poorly perfused tissues, therefore we evaluated the impact of these changes on model outputs. After looking at the duration and concentration at the end of the distribution phase, elimination rate, AUC, maximum concentrations, number of days to steady state, and time elapsed for 90% of chemical eliminated, we found that the only significant change in model outputs is in the duration of the distribution phase. The richly/poorly perfused correction doubled the duration of the distribution phase while the duration for the blood volume correction was ¾ of the original. We also determined that the effective volume of distribution is at least twice the predicted value for 153 of the chemicals, independent of the correction. Overall, comparison to <I>*in vivo*</I> data identified discrepancies that we reduced by refining our phospholipid partitioning and plasma binding models, which improved the accuracy of the partition coefficient predictions. However, separation of the rest of body into richly/poorly perfused compartments and consideration of blood volumes only made a significant difference in the duration of the distribution phase. <I>*This abstract does not necessarily reflect U.S. EPA policy*</I>.