High-Throughput Physiologically Based Toxicokinetic Models for ToxCast Chemicals

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Physiologically based toxicokinetic (PBTK) models aid in predicting exposure doses needed to create tissue concentrations equivalent to those identified as bioactive by ToxCast. We have implemented four empirical and physiologically-based toxicokinetic (TK) models within a new R software package, vLiverPBPK. For the thousands of chemicals without *in vivo* TK data, all four TK models were designed to be parameterized with high-throughput (HT) *in vitro* TK experiments and structure-based physico-chemical property predictions. Two general types of predictions – steady-state serum concentration resulting from repeated exposures for use in reverse toxicokinetic (RTK) studies, and prediction of TK time course metrics such as C_{max} and time-integrated plasma concentration (Area Under the Curve or AUC) for evaluating model prediction by comparison to *in vivo* data. In predicting the concentrations of a chemical over time, the HTTK models primarily use *in vitro* data for both the fraction of chemical unbound to plasma and the hepatic clearance, as well as structure-derived physicochemical properties for the calculation of partition coefficients and ratios of blood flows and tissue volumes to body weight for the models with multiple compartments. We have performed simulation studies using the more sophisticated HTPBTK model to evaluate key assumptions in the simpler three-compartment, steady-state model used in previous RTK studies and have found that although the majority of chemicals reach steady state within seven weeks, some never reach steady state within a typical human lifespan. We were also able to predict average steady state concentrations resulting from discrete dosing with predictions based on the infusion dosing assumption used in previous RTK studies; many of the chemicals that quickly reached lower steady state concentrations reached maximum concentrations of more than double the average steady state concentration. The package can currently make predictions for369 chemicals, including 75 pharmaceuticals and 294 ToxCast chemicals. We will use the package to distribute additional data as it becomes available. *This abstract does not necessarily reflect US EPA policy.*