Applying a High-Throughput PBTK Model for IVIVE

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The ability to link *in vitro* and *in vivo* toxicity enables the use of high-throughput *in vitro* assays as an alternative to resource intensive animal studies. Toxicokinetics (TK) should help describe this link, but prior work found weak correlation when using a TK model for *in vitro-in vivo* extrapolation (IVIVE) (Wetmore *et al.*, 2013). In this work, we evaluated the assumptions in the use of a high-throughput, physiologically based (PBTK) model to relate *in vitro* and *in vivo* toxicity data. The generic, high-throughput PBTK model in this study used rat *in vitro* measured values of fraction unbound in plasma (f_{up}) and intrinsic hepatic clearance for 92 chemicals. *In vivo* doses (endpoint-specific low effect levels for rat, EPA's ToxRefDB) were transformed to concentrations (x_{PBTK}) via the PBTK model, and compared with *in vitro* AC_{50} (EPA's ToxCast program, 394 assays) relative to a randomly parameterized result (x_{rand}) and untransformed dose (x_{dose}). For each pair of *in vitro* assay and *in vivo* response, simple regressions were performed of standardized AC_{50} vs the three separate predictors: x_{PBTK}, x_{rand}, and x_{dose}. Different combinations of assumptions in the use of the PBTK model were then evaluated based on how frequently (F_{PBTK}, F_{rand}, F_{dose}) a predictor had the largest absolute slope. The best result for the PBTK model was achieved by using maximum plasma concentration and assuming metabolism independent of f_{up} (F_{PBTK} = 82 %, F_{rand} = 7 %, and F_{dose} = 11 %). Using *in vitro* free vs nominal concentration also improved results for cell based assays (F_{PBTK} = 87 % vs 78 %). Results demonstrate that use of the PBTK model improves the correlation between the *in vitro* and *in vivo* toxicity data relative to the untransformed dose and the randomized result in the rat. This suggests that incorporating TK may enhance human IVIVE.

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This abstract may not reflect U.S. EPA policy.