High Throughput Pharmacokinetics for Environmental Chemicals

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Pharmacokinetic (PK) models are critical to determine whether chemical exposures produce potentially hazardous tissue concentrations. For bioactivity identified *in vitro* (*e.g.* ToxCast) – hazardous or not – PK models can forecast exposure thresholds, below which no significant bioactivity is expected. Successful methods have been developed for pharmaceutical compounds to determine PK from limited *in vitro* measurements and chemical structure-derived property predictions. These high throughput (HT) PK methods provide a more rapid and less resource–intensive alternative to traditional PK model development. Unfortunately, predictions from HTPK approaches have demonstrated mixed success for environmental chemicals when compared to predictions made by PK models developed with extensive *in vivo* data. Here we tested assumptions of previous HTPK approaches using a simple physiologically-based PK (PBPK) model and *in vitro* data for 232 chemicals in human and 39 chemicals in rat. We then analyzed the discrepancy between the predictions of HTPK and *in vivo* literature PK data for 44, mostly pharmaceutical, chemicals, using the method of best subsets to identify those properties that correlate with poor predictive ability (*e.g., in vitro* HTPK data, physico-chemical descriptors, chemical structure, and predicted transporter affinities). We propose a framework for PK triage in stages: First, *in vitro* measurements and *in silico* predictions determine whether the simplest HTPK approaches are likely to be sufficient. Then identify and collected any additional, targeted *in vitro* data that is needed. Finally, identify those chemicals most likely to require traditional, *in vivo* PK methods. This methodology allows prioritization of PK resources and characterizes the confidence in HTPK model predictions for potentially thousands of environmental chemicals that currently have no PK data. *This abstract does not necessarily reflect EPA policy.*