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High-throughput PBPK and Microdosimetry: Cell-level Exposures in a Virtual Tissue Context

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Toxicokinetic (TK) models can determine whether chemical exposures produce potentially hazardous tissue concentrations. Tissue microdosimetry TK models relate whole-body chemical exposures to cell-scale concentrations. As a proof of concept, we approximated the micro-anatomic architecture of the hepatic lobule with a discrete topology by a graphical model that can be connected to a chemical-specific physiologically-based TK (PBTK) model. The development of traditional PBTK models is time and resource intensive. Successful methods have been developed for pharmaceutical compounds to determine TK from limited *in vitro* measurements and chemical structure-derived property predictions. These high throughput (HT) TK methods provide a more rapid and less resource–intensive alternative to traditional TK model development. We have augmented these *in vitro* data with chemical structure-based descriptors and mechanistic tissue partitioning models to construct HTPBPK models for over three hundred environmental and pharmaceutical chemicals. When evaluated with human *in vivo* data for 74 chemicals we find that we can generally predict when HTPBPK models will perform well, and when more complicated effects (*e.g.*, transporters) impact HTPBPK assumptions. For those chemicals where the assumptions that allow HTPBPK models are appropriate, virtual tissue simulation of quantitative chemical-specific effects is possible. *This abstract does not necessarily reflect Agency policy.*