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Presentation Title: High Throughput PBPK: Evaluating EPA's Open-Source Data and Tools for Dosimetry and Exposure Reconstruction
Presentation Description: New technologies and in vitro testing approaches have been valuable additions to risk assessments that have historically relied solely on in vivo test results. Compared to in vivo methods, in vitro high throughput screening (HTS) assays are less expensive, faster and can provide mechanistic insights on chemical action. However, extrapolating from in vitro chemical concentrations to target tissue or blood concentrations in vivo is fraught with uncertainties, and modeling is dependent upon pharmacokinetic variables not measured in in vitro assays. To address this need, new tools have been created for characterizing, simulating, and evaluating chemical biokinetics. Physiologically-based pharmacokinetic (PBPK) models provide estimates of chemical exposures that produce potentially hazardous tissue concentrations, while tissue microdosimetry PK models relate whole-body chemical exposures to cell-scale concentrations. These tools rely on high-throughput in vitro measurements, and successful methods exist for pharmaceutical compounds that determine PK from limited in vitro measurements and chemical structure-derived property predictions. These high throughput (HT) methods provide a more rapid and less resource–intensive alternative to traditional PK 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 HTPBPK model assumptions are appropriate, virtual tissue simulation of quantitative chemical-specific effects is possible. By comparison to experimental in vivo data, we estimate for which chemicals these tools may be used with confidence, and identify those chemicals where alternative approaches are needed. We have organized all available TK data into a computable format used as part of an R package "httk" which freely available on the Comprehensive R Archive Network (CRAN). Ongoing research is identifying the domain of applicability of these data and models. *This abstract does not necessarily reflect the views of the US EPA.*