Using In Vitro Data and PBPK Models to Predict Inhalation Toxicity

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In vitro assay data can be used to predict safe chemical exposure levels when combined with reverse dosimetry that utilizes pharmacokinetic data. We conducted a proof-of-concept study to evaluate using non-animal approaches to inform inhalation hazard identification and assessment. We selected 20 volatile organic compounds (e.g., styrene, tetrachloroethylene) for evaluation based on abundance of pharmacokinetic data and availability of published minimal risk levels derived from inhalation exposure studies. We obtained from public databases activity concentrations that were derived from in vitro assays measuring diverse endpoints (e.g., genotoxicity, cytochrome p450 activation, transcriptome analysis). Using these data, reverse dosimetry was performed with open-source and commercial PBPK modeling tools to estimate daily equivalent administered doses (EADs) that would result in plasma and lung concentrations equivalent to the in vitro activity concentrations. The EADs were then compared to the in vivo point of departure (POD) or published minimal risk levels. Our preliminary results showed that the estimated EADs based on lung concentration were closer to in vivo PODs than those based on plasma concentration for most chemicals. The differences between EADs and in vivo data varied greatly among chemicals and across assays. The EADs estimated using in vitro assays measuring endpoints more mechanistically relevant to in vivo toxicity better predicted in vivo PODs than EADs estimated using in vitro assays measuring nonspecific effects (e.g., cytotoxicity assays). This project demonstrates a promising approach for predicting inhalation toxicity using non-animal approaches. This project was funded by NIEHS under Contract No. HHSN273201500010C.