Combining NAM Data and IVIVE for Evaluating Potential Inhalation Toxicity

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Traditional chemical risk assessment is often based on no- or lowest-observed-adverse-effect levels derived from in vivo toxicity data. New approach methodologies, such as in vitro systems, can be used for toxicity screening in a more rapid and cost-effective manner than animal tests. In vitro assays can provide safe exposure levels for a chemical when combined with an in vitro to in vivo extrapolation (IVIVE) approach. IVIVE uses pharmacokinetic models to relate concentrations of substances that induce in vitro responses to a corresponding equivalent in vivo dose. In this study, we selected 20 volatile organic compounds (e.g., styrene, tetrachloroethylene, 2-butoxyethanol) with abundant pharmacokinetic data and published minimal risk levels (MRLs) covering multiple target organs via inhalation exposure. We obtained activity concentrations derived from in vitro assays measuring diverse endpoints (e.g., genotoxicity, cytochrome p450 activation, transcriptome analysis) from public resources. Using these data, IVIVE was performed to estimate the daily equivalent administered dose (EAD) that would result in plasma and lung concentrations equivalent to the in vitro activity concentrations. For chemicals that were inactive in an in vitro assay, the maximum testing concentration was used for IVIVE. The EADs were then compared to the in vivo point of departure (POD) used to derive the MRLs. Our preliminary results showed that the agreement between EADs and in vivo data varies greatly between chemicals and across assays, ranging from less than 2-fold to more than 1000-fold different. For most chemicals, the EADs estimated based on lung concentration were more comparable to in vivo PODs than those based on plasma concentration. Furthermore, the EADs estimated using an in vitro assay that measures an endpoint more mechanistically relevant to in vivo exposure better predicted in vivo PODs compared to those estimated using an in vitro assay measuring nonspecific effects (e.g., cytotoxicity assays). The impact of metabolism and pharmacokinetic model structures on IVIVE outcomes were also evaluated. In summary, this study provides proof-of-concept case examples to illustrate the utility of using non-animal approaches to inform hazard identification and risk for humans exposed to inhaled substances.
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