An Open-source, Generalized Workflow for IVIVE Analysis

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A critical challenge for implementing non-animal approaches for chemical safety testing is to translate in vitro assay results to potential in vivo effects. To address this challenge, we have developed an open-source in vitro to in vivo extrapolation (IVIVE) workflow. The workflow incorporates in vitro data, quantitative structure-property relationship (QSPR) predictions, and one-compartment pharmacokinetic (PK) or multi-compartment physiologically based PK (PBPK) models to predict in vivo exposures that would result in blood concentrations equivalent to in vitro activity concentrations. We previously applied the IVIVE-PK workflow to evaluate estrogenic activity for environmental chemicals and observed good concordance between in vitro and in vivo dosimetry. However, for chemicals with poor oral bioavailability (e.g., bisphenol A, 17β-estradiol), the IVIVE-PK workflow tended to underestimate in vivo exposure levels, possibly due to a lack of extrahepatic metabolism in the one-compartment PK model. In this study, we developed a multi-compartment PBPK model that includes gastrointestinal glucuronidation to simulate a chemical's plasma and tissue concentration after oral administration. We incorporated this PBPK model into the IVIVE workflow (IVIVE-PBPK) to estimate equivalent administered in vivo dose levels based on in vitro estrogenic activity concentrations for bisphenol A and 17β-estradiol, both of which are known to undergo glucuronidation, and achieved improved results. To apply this IVIVE-PBPK workflow to a larger chemical space, we also developed in silico models to predict kinetic constants for glucuronidation and other pharmacokinetic parameters. The IVIVE-PBPK workflow will be available via the NICEATM Integrated Chemical Environment (ICE) at https://ice.ntp.niehs.nih.gov, and a wide range of in vitro data within ICE, including curated Tox21 data, are available for workflow input. This optimized approach for using in vitro data to quantitatively predict in vivo effects is presented via an online tool that is accessible to a diverse stakeholder community and is designed to increase the utility of in vitro data in risk assessment applications. This project was funded with U.S. federal funds from the NIEHS/NIH/HHS under Contract HHSN273201500010C.

Keywords: physiologically-based pharmacokinetics, glucuronidation, in vitro to in vivo extrapolation