Open Source Workflows for In Vitro to In Vivo Extrapolation

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In vitro to in vivo extrapolation (IVIVE) facilitates comparison of effects observed in in vitro assays to effects observed in in vivo animal tests. An IVIVE analysis estimates the daily equivalent administered dose (EAD) that produces the in vivo plasma or tissue concentration equivalent to an in vitro effective concentration. IVIVE analyses have been conducted using both simple one-compartment pharmacokinetic (PK) models and more complex physiologically based pharmacokinetic (PBPK) models. However, many commonly used modeling tools are proprietary software that lack the transparency needed to verify values and share results. Here we present workflows for IVIVE analysis using both simple PK and PBPK models, built with two open-source platforms. The Konstanz Information Miner (KNIME) platform uses a modular data pipeline concept with a graphical user interface for data analysis and visualization. The Jupyter Notebook platform provides additional user flexibility by providing both human-readable notebook documents and executable documents viewable via a web browser and dashboard. To predict an EAD using IVIVE workflows containing one-compartment PK models, the only inputs required on either platform are the in vitro assay active concentration (expressed, for example, as half-maximal activity concentration or AC50), and three PK parameters: fraction of chemical unbound to protein, intrinsic clearance, and renal clearance. For users that do not have their own values for these PK parameters, our workflow provides experimental values for 448 chemicals and values predicted from structure-based models for more than 7600 chemicals. IVIVE workflows using a generalized PBPK model require additional PK parameters (e.g., tissue partition coefficients that can either be experimentally measured or predicted). Our presentation will include two examples, one focusing on estrogenic activity and the other focusing on developmental toxicity, to demonstrate how the workflows provide a simple and fast approach to IVIVE analysis. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN273201500010C.*

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