An Open-Source Workflow for *In Vitro* to *In Vivo* Extrapolation

X Chang[1], J Pirone[1], SM Bell[1], D Allen[1], W Casey[2], N Kleinstreuer[2]

[1]ILS, RTP, NC, USA; [2]NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA

In vitro to *in vivo* extrapolation (IVIVE) facilitates the comparison of effects observed in *in vitro* assays to effects observed in *in vivo* animal tests by correlating an *in vitro* effective concentration to *in vivo* plasma or tissue concentrations. We previously used a population-based pharmacokinetic (PK) model to estimate the daily equivalent administered dose of a test chemical that would result in a steady-state blood concentration equivalent to the concentration of that chemical that induces a response in an *in vitro* estrogen receptor transactivation assay. To make the model publicly accessible and broadly applicable, we have constructed model workflows using two open-source platforms, Konstanz Information Miner (KNIME) and Jupyter Notebook. KNIME uses a modular data pipeline concept with a graphical user interface that allows assembly of modules for data preprocessing, modeling, analysis and visualization. To run our IVIVE workflow, the only inputs required are the *in vitro* assay active concentrations (e.g., half-maximal activity concentrations, AC50s) and relevant PK parameters that affect ADME (absorption, distribution, metabolism, and excretion), which are fraction of chemical unbound to protein, intrinsic clearance, and renal clearance. Although experimental PK parameter values are preferred, and are currently available for 448 chemicals, predicted values can be used if necessary. Our workflow provides predicted PK parameters derived from structure-based models for more than 7600 chemicals. The Jupyter Notebook IVIVE workflow uses the same variable inputs, but provides additional user flexibility via a web browser and dashboard. Users can access human-readable notebook documents containing the analysis description and the results (e.g. tables, figures), as well as executable documents which can be run to perform the IVIVE analysis. This presentation provides two examples of using the workflows, one focusing on assays measuring estrogenic activity and the other focusing on developmental toxicity, to demonstrate how they provide a fast and easy approach to IVIVE analysis. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN273201500010C.*

Presenting author: Xiaoqing Chang, changx@niehs.nih.gov