

## **An Open Source IVIVE Workflow Integrating In Vitro Data, QSAR Models and Reverse Dosimetry**

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A critical challenge to implementing non-animal approaches for chemical safety testing is linking in vitro assay results to potential in vivo effects. To address this challenge, we developed an in vitro to in vivo extrapolation (IVIVE) workflow incorporating in vitro data, QSAR models, and reverse dosimetry with a population-based one-compartment pharmacokinetic (PK) model. The resulting workflow is available through NICEATM's Integrated Chemical Environment web resource, and can be used as an interactive online tool or downloaded to run locally. The workflow allows estimation of steady-state blood concentration ( $C_{ss}$ ) across a simulated population following a given dose. It also allows prediction of the external dose leading to a  $C_{ss}$  equivalent to effective concentration in user-selected in vitro assays. Where data are available, the predicted external dose can be compared to in vivo experimental doses for the same chemical. This comparison can be used to establish confidence in the model's performance when generating predictions for structurally related compounds lacking in vivo data. Users can supply PK parameters (e.g., fraction unbound to plasma protein, hepatic clearance), or parameters can be predicted based on chemical structures using OPERA's QSAR models. Using the estrogen receptor pathway as an example, we will demonstrate how the IVIVE workflow can be used to evaluate the correlation between in vitro and in vivo dosimetry for toxicologically relevant endpoints. This was funded with U.S. federal funds from NIEHS/NIH/HHS under Contract HHSN273201500010C.