Computational Support of Pharmacokinetic Models and In Vitro to In Vivo Extrapolation

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Pharmacokinetic models and in vitro to in vivo extrapolation (IVIVE) allow researchers to predict the in vivo distribution and bioactivity of toxicants by quantitatively relating in vitro results to in vivo systems. By translating in vitro experimental concentrations into relevant in vivo doses, these nonanimal alternative test methods have the potential to inform regulatory decisions by providing a margin of exposure context. Additionally, pharmacokinetic models can inform hazard screening prioritization by estimating tissue-level concentrations to characterize the distribution of bioactive compounds. Quantitative structure-activity/property relationship modeling tools such as the OPEn structure-activity/property Relationship App have broadened the applicability of physiologically based pharmacokinetic (PBPK) and IVIVE analyses by extending the range of potential chemical analytes to all substances with defined structures. To further expand the transparency and accessibility of PBPK and IVIVE models, we have developed open-access computational tools to facilitate customized simulations and analysis. The National Toxicology Program's Integrated Chemical Environment includes graphical user interface tools for both PBPK modeling and IVIVE that allow users to specify the model complexity, species of interest, exposure route, dosing regimen, simulation time, and any relevant in vitro assay data. These tools provide a well-documented, easy-to-understand platform to apply PBPK and IVIVE modeling to chemicals of interest. Future applications of these tools and techniques may provide valuable insight for regulatory decision making. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.