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

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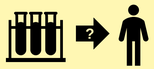
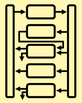
Highlights



Interpreting in vitro data requires in vivo context



PBPK models & IVIVE can help

Computational tools democratize IVIVE

Introduction

- New approach methodologies (NAMs) such as in vitro assays and computational approaches seek to inform risk assessment while reducing dependence on animal testing.
- In vitro assays are typically mechanistic measures of bioactivity and need in vivo context to aid interpretation.
- Physiologically based pharmacokinetic (PBPK) models estimate in vivo plasma and tissue concentrations from external doses.
- In vitro to in vivo extrapolation (IVIVE) leverages PBPK models to estimate the in vivo equivalent administered dose (EAD) using assay concentrations.
- The integrated chemical environment (ICE) is an open-access tool to facilitate PBPK and IVIVE analyses.
- We demonstrate the application of PBPK and IVIVE analyses and how advancements in computational support tools provide transparency, applicability, and accessibility.

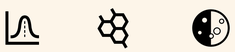
Data and Parameter Sources

PBPK Parameters

Physiological

- httk R package includes generalized parameters[1]

Pharmacokinetic (PK)



- QSAR prediction software such as OPERA fills gaps[2]

In Vitro Bioactivity Data

Assay Results

- Tox21[3] and ToxCast[4] high throughput screening (HTS)

Quality Controls

- ICE includes curated HTS data[5] for IVIVE analysis

PBPK Case Study

ICE User Interface

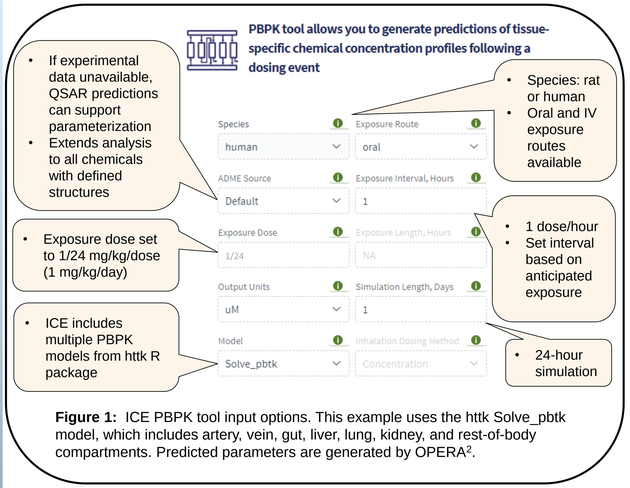


Figure 1: ICE PBPK tool input options. This example uses the httk Solve_pbtk model, which includes artery, vein, gut, liver, lung, kidney, and rest-of-body compartments. Predicted parameters are generated by OPERA[2].

ICE Output: PBPK Predictions

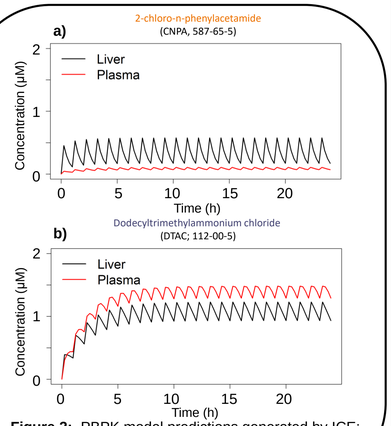


Figure 2: PBPK model predictions generated by ICE; Liver and plasma compartments shown. DTAC shows accumulation due to low metabolic clearance.

IVIVE Case Study

PBPK Modeling and IVIVE

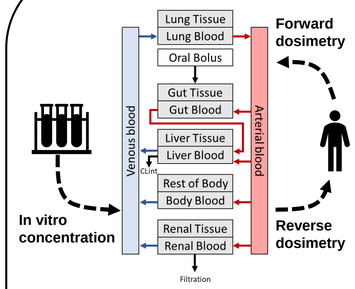


Figure 3: The role of PBPK modeling in IVIVE. In vitro bioactivity concentration is used to represent plasma concentrations that may result in similar bioactivity. Reverse dosimetry using PBPK models predicts human EAD that would produce equivalent plasma concentrations to in vitro activity.

Case Study:

- PBPK inputs represent above case study (Figure 1)
- Dose is assumed to be 1 mg/kg/day with 1 dose per hour for 24 hours

- "Cell viability process" assay AC50s from the ICE curated HTS data set are selected

Integrated Chemical Environment

ICE Output: ADME Impacts on EAD

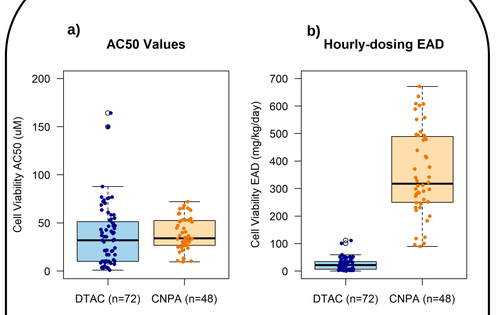
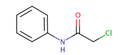


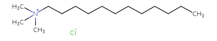
Figure 4: a) In vitro AC50 and b) IVIVE results for DTAC and CNPA generated by ICE. While AC50 values were similar across chemicals, DTAC has lower relative EAD values (b) due to the model estimating higher accumulation of DTAC in the blood compared with CNPA (Figure 2).

Case Study Design

- Considered two example chemicals with different PK properties but similar in vitro activity for a toxicity endpoint (cell viability).



2-chloro-n-phenylacetamide
(CNPA, 587-65-5)



Dodecyltrimethylammonium chloride
(DTAC; 112-00-5)

- Used ICE[5] to demonstrate how open-access tools democratize PBPK and IVIVE analyses

Conclusions

- Current PBPK modeling and IVIVE support tools:
  - Provide transparency through open-source calculations.
  - Expand applicability across chemicals with defined structures through read-across approaches.
  - Are publicly available and easily accessed through the ICE web user interface (https://ice.ntp.niehs.nih.gov/).
- PBPK modeling can estimate tissue level exposures from in vivo regulatory studies to identify chemical distributions and relevant bioactivity (Figure 2).
- IVIVE provides in vivo context for in vitro results and can inform chemical prioritization or margin-of-exposure analyses.
- Our case study highlights how similar in vitro results may have different implications for EADs based on ADME considerations (Figure 4).
- These NAMs have potential to supplement or replace traditional methodologies for regulatory toxicity testing

References & Acknowledgments

[1]Pearce et al. 2017. httk: R Package for High-Throughput Toxicokinetics. J Stat Softw 79.
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[5]Bell et al., 2020. An integrated chemical environment with tools for chemical safety testing. Toxicol. In Vitro 67, 104916.

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