National Institute of Environmental Health Sciences
Division of the National Toxicology Program

Integrating Parameter Uncertainty in PBPK Modeling

Abstract ID #16

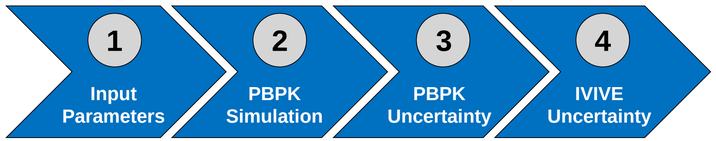
David Hines[1], Jaleh Abedini[1], Dave Allen[1], Nicole Kleinstreuer[2], Kamel Mansouri[2]

[1]Inotiv, Research Triangle Park, NC, USA; [2]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, USA

Introduction

- Physiologically based pharmacokinetic (PBPK) models rely on chemical-specific parameters to predict internal concentrations or generate in vitro to in vivo extrapolation (IVIVE) estimates.
- Input parameters can be empirically measured or estimated through in silico approaches such as quantitative structure-activity relationship (QSAR) models.
- Uncertainty and variability are inherent in both empirical and *in silico* parameters, as experimental variability (e.g. interlaboratory effects) impacts empirical measures as well as in silico predictions trained with empirical data.
- This uncertainty in input parameters propagates through PBPK calculations to result in uncertainty in model predictions.
- This study evaluated how parameter uncertainty impacts PBPK predictions using the OPEn quantitative structure-activity/property Relationship App (OPERA v2.7), which provides QSAR parameter predictions as well as estimates of uncertainty in the form of a range around each prediction value.

Methods



1 Input Parameters

- Can be empirical or predicted: we used QSAR parameters predictions generated by OPERA v2.7 (Mansouri et al. 2018).
- OPERA provides a confidence range around each prediction as an estimate of uncertainty.
- Parameters included intrinsic clearance, fraction unbound, pka, logP, and Henry's Law constant.

2 PBPK Simulation

- PBPK simulations were run using the solve_pbtk model from the httk R package (Pearce et al. 2017).
- Modeling simulated a 1 mg/kg dose via oral gavage in humans.
- Pharmacokinetic profiles and area under the curve (AUC) were recorded for plasma.

3 PBPK Uncertainty

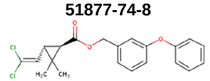
- Parameters were systematically tested to identify the sets that maximized and minimized PBPK plasma concentration predictions.
- Plasma concentrations were highest when all parameter values were minimized.

4 IVIVE Uncertainty

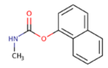
- QSAR parameter uncertainty implications for IVIVE were examined by applying the full range of maximum plasma concentrations (Cmax) to calculate equivalent administered dose (EAD) for in vitro data from the Integrated Chemical Environment (ICE; Abedini et al. 2021).

Case Study

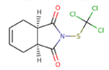
Permethrin
51877-74-8



Carbaryl
63-25-2



Captan
133-06-2



- Three pesticides were selected that represented diversity in structure and entire QSAR prediction range (see table below).
- In vitro bioactivity data used for IVIVE (AC50 values) were obtained from ICE.

Pesticide	Intrinsic Clearance*	Fraction Unbound	pKa	LogP	Log Henry's Law
(+)-trans-Permethrin ("Permethrin")	68.39 [57.83 : 87.59]	0.01 [0.01 : 0.01]		6.49 [6.46 : 6.54]	-7.6 [-9.5 : -5.7]
Carabyl	27.27 [26.17 : 28.37]	0.69 [0.67 : 0.69]	8.1 [7.1 : 9.1] donor	2.35 [2.32 : 2.41]	-7.8 [-8.9 : -6.7]
Captan	0.01 [0.01 : 1.98]	0.08 [0.01 : 0.18]	2.1 [-1.3 : 5.4] acceptor	2.80 [2.75 : 2.85]	-5.4 [-6.3 : -4.5]

*QSAR parameters (range). Intrinsic clearance is in units of uL/min/10^6 hepatocytes. The other parameters are unitless.

Results

Fig 1: Pharmacokinetic Profiles

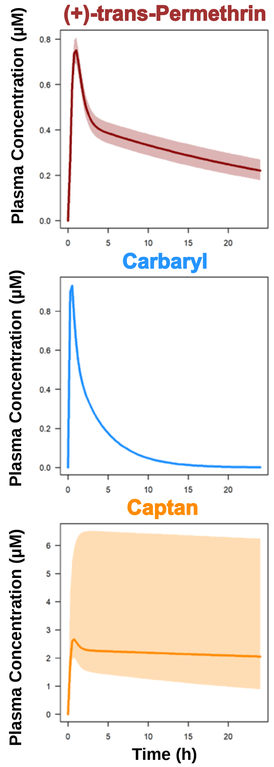


Fig 2: Plasma AUC

Plasma AUC predictions based on OPERA predicted value (dot) and range (bars).

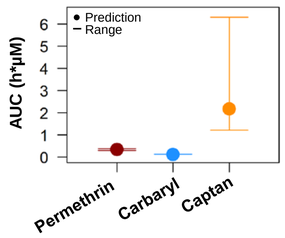
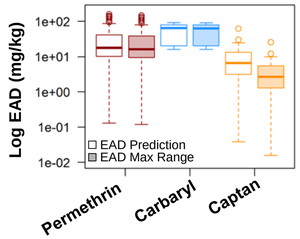


Fig 3: IVIVE

Distributions of EAD values based on ICE data. Filled boxes show the effect of input uncertainty.



- Carbaryl had the narrowest range of PBPK results based on QSAR parameter prediction ranges, followed by Permethrin and Captan (Figs 1 and 2).
- Fraction unbound, intrinsic clearance, and logP were the input parameters with the most potential for influence on PBPK model outputs (e.g. Captan).

Parameter/ condition	Biochemical implication	Effect on PBPK plasma prediction
Fraction unbound ↑	High bioavailability in plasma can facilitate rapid clearance	Cmax, AUC ↓
Intrinsic clearance ↑	High enzymatic activity rapidly clears chemical	Cmax, AUC ↓
LogP ↑	Highly lipophilic compound accumulates in lipid-rich tissues	Cmax, AUC ↓

- Application of the Cmax range maximum to IVIVE calculations resulted in more conservative EAD estimates informed by QSAR prediction ranges (60.2% lower for Captan; Fig 3).

Discussion

- Quantification of uncertainty in PBPK outputs from input parameter variability can help researchers characterize confidence in model results.
- Estimating the variability and uncertainty inherent in empirically measured and QSAR predicted parameters, then using the ranges of parameters to generate prediction ranges is a way to describe possible PBPK outcomes based on the best available knowledge.
- The case study in this work demonstrates how the QSAR parameter prediction ranges generated by OPERA can be used with this approach to characterize the effects of input parameter variability.
- The magnitude of input parameter effects can vary with other parameter values. For example, both Permethrin and Captan have ranges of fraction unbound values near zero, but Captan has substantially higher plasma AUC values due to its lower intrinsic clearance and LogP parameters.
- Quantifying how input parameter uncertainty propagates through PBPK models can inform more conservative approaches to applications such as IVIVE.

Take-Home Points

- Experimental variability results in uncertainty that is inherent in both empirical and in silico predicted PBPK input parameters.
- Calculating ranges of PBPK model outputs based on input parameter ranges can characterize the effects of input parameter variability.
- Characterization of parameter variability facilitates better informed interpretation of model results.

References

Abedini et al. 2021. Application of new approach methodologies: ICE tools to support chemical evaluations. Computational Toxicology, 20:100184.

Mansouri et al. 2018. OPERA models for predicting physicochemical properties and environmental fate endpoints. Journal of Cheminformatics, 10(1):1-19.

Pearce et al. 2017. Httk: R package for high-throughput toxicokinetics. Journal of Statistical Software, 79(4):1.

Acknowledgments

This project was funded by the National Institute of Environmental Health Sciences, National Institutes of Health under Contract No. HHSN273201500010C. The authors declare no conflict of interest. The views expressed do not necessarily represent the positions of any federal agency.