National Institute of Environmental Health Sciences
Division of Translational Toxicology

Physiologically Based Pharmacokinetic (PBPK) Modeling Approach to Quantify Chemical Distribution in Brain and Adipose Compartments

A. Unnikrishnan[1], X. Chang[1], A. Kreutz[1], T. LaPratt[1], J. P. Sluka[3], D. Li[4], M. Linakis[5], E. Reinke[1], H.T. Hogberg[2], N. Kleinstreuer[2,6]

[1]Inotiv, United States; [2]NIH/NIEHS/DTT/NICEATM, United States; [3]Indiana University, United States; [4]University of Nevada, United States; [5]Ramboll, United States; [6]NIH/OD/DPCPSI, United States

Introduction

- Physiologically based pharmacokinetic (PBPK) models represent absorption, distribution, metabolism, and excretion (ADME) processes to predict concentrations of chemicals in relevant tissues. PBPK models are based on various assumptions and simplifications to make them computationally tractable.
- The U.S. Environmental Protection Agency's (EPA's) high-throughput toxicokinetics (httk) R package [1] provides open-source PBPK models that can accommodate integration of new compartments.
- While the httk package includes a number of compartments representing organs and organ systems, it lacks compartments for brain and adipose tissues. These are of interest to predict neurotoxicity potential and likelihood of bioaccumulation.
- We have added brain and adipose compartments to the httk package (version 2.2.2) to estimate chemical concentrations in these tissues.

Workflow

- The workflow below was used to develop a simple and a complex model:
  - The simple perfusion-limited model facilitates parameterization with limited data and assumed linear clearance.
  - The complex diffusion-limited model accounts for chemical transfer across the blood-brain barrier.

IDENTIFY
- Model structure
- Model equations
- Model parameters

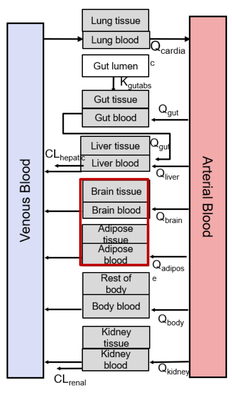
GENERATE
- File representing a description of the model.
- C translation file created using GNU MCSim simulation package [2].
- R programming functions for model information, chemical-specific parameters, and model simulation.

EXECUTE
- Model building
- Model output
- Model evaluation

* Workflow based on [3].

Perfusion-Limited Model With Brain and Adipose Compartments (Simple Model)

Model Structure



Equations for Brain and Adipose Model

$$\frac{dA_{brain}}{dt} = Q_{brain}\left(C_{art} - \frac{C_{brain} \cdot R_{b2p}}{K_{brain2pu} \cdot f_{up}}\right)$$

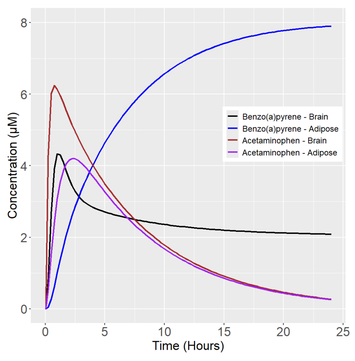
$$\frac{dA_{adipose}}{dt} = Q_{adipose}\left(C_{art} - \frac{C_{adipose} \cdot R_{b2p}}{K_{adipose2pu} \cdot f_{up}}\right)$$

$$Q_{tissue} = Q_{cardiac} \cdot Q_{tissuef}$$

A_i : amount in tissue i
Q_i : blood flow to tissue i
f_{up} : unbound fraction in plasma
R_{b2p}: blood-to-plasma concentration ratio
$K_{tissue2pu}$: tissue-to-plasma partition coefficient
$Q_{tissuef}$: fraction of blood flow to tissue out of total cardiac output

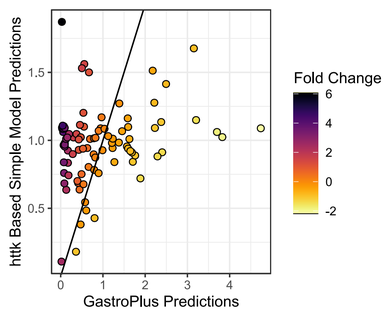
Perfusion-Limited Model Output

Concentration vs. Time



Model "chemical concentration vs. time (CvT)" output using a generic dosing regimen of 1 mg/kg daily oral dose in human showed higher accumulation in adipose vs. brain.

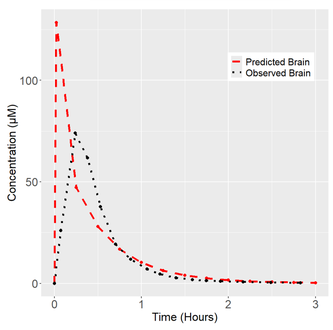
Comparison with Commercial Model



For 91 potential developmental neurotoxicants, predictions of brain Cmax (maximum concentration) generated by the simple model were within 10-fold of those generated by the commercial GastroPlus® model [4].

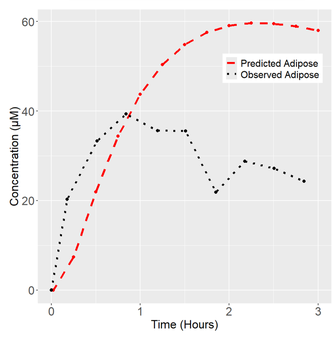
Acetaminophen - Comparison with Observed Data

Brain Compartment



Dosing regimen: daily dose = 16 mg/kg, days = 1, doses per day = 1, species = rat, route = IV

Adipose Compartment

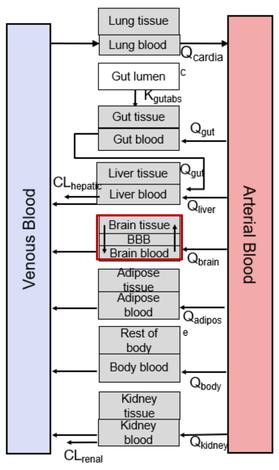


Dosing regimen: daily dose = 14.2 mg/kg, days = 1, doses per day = 1, species = human, route = oral

For acetaminophen, predictions for both brain and adipose compartments show general concordance with observed data from literature. The observed data and model output also suggest a certain degree of accumulation in adipose tissue.

Diffusion-Limited Model Considering Blood-Brain Barrier Kinetics (Complex Model)

Model Structure



Equations for Complex Brain Model

- The movement of chemicals from capillary blood to the cellular matrix of the brain tissue is proportional to the permeability-surface area product. This can be expressed as a proportion of the blood flow Q_{brain}, modulated by the blood-brain barrier (BBB) permeability coefficient.
- The BBB permeability coefficient calculation utilized measured or predicted permeability values via transwell assays (P_e) [5].

$$\frac{d}{dt}A_{brain,b} = Q_{brain} \cdot (C_{art} - C_{brain,b}) - K_{pbbb} \cdot Q_{brain} \cdot (C_{brain,b} - \frac{C_{brain} \cdot R_{b2p}}{K_{brain2pu} \cdot f_{uP}})$$

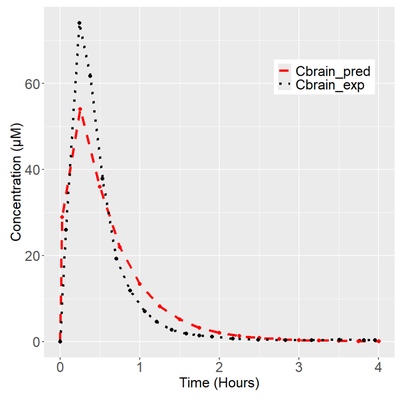
$$\frac{d}{dt}A_{brain} = K_{pbbb} \cdot Q_{brain} \cdot \left(C_{brain,b} - \frac{C_{brain} \cdot R_{b2p}}{K_{brain2pu} \cdot f_{up}}\right)$$

$$K_{pbbb} = min((P_e \cdot Area_{brain})/Q_{brain}, 1)$$

$A_{brain,b}$: amount of chemicals in capillary blood of brain
A_{brain} : amount of chemicals in brain tissue
C_{brain} : concentration of chemical in brain tissue
$C_{brain,b}$: concentration of chemicals in capillary blood of brain
P_e: effective permeability coefficient from a transwell assay
K_{pbbb}: permeability coefficient between capillary blood and brain

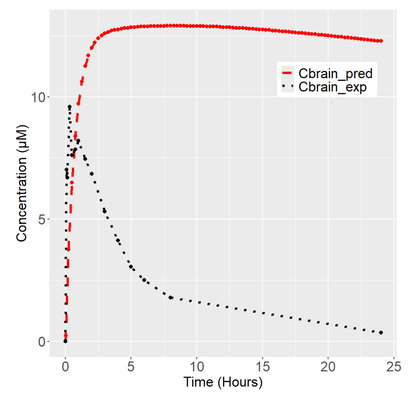
Diffusion-Limited Model Output

Brain - Acetaminophen (Hydrophilic)



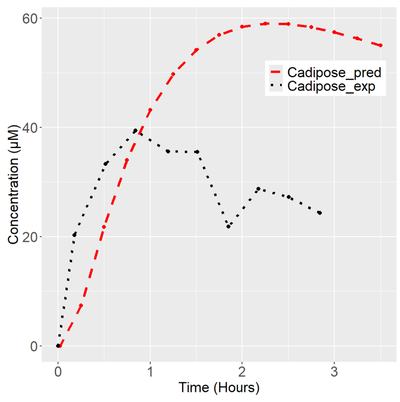
Kpbbb = 0.12, Octanol-Water Partition Coefficient = 0.46
Dosing regimen: daily dose = 16 mg/kg, days = 1, doses per day = 1, species = rat, route = IV

Brain - Benzo(a)pyrene (Lipophilic)



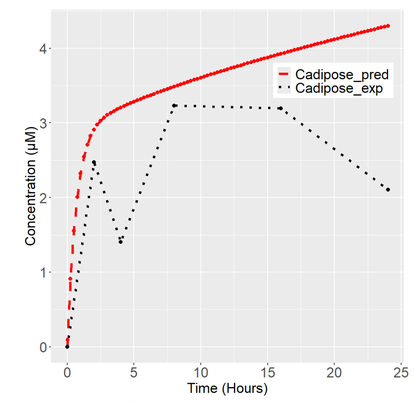
Kpbbb = 1, Octanol-Water Partition Coefficient = 6.13
Dosing regimen: daily dose = 2 mg/kg, days = 1, doses per day = 1, species = rat, route = IV

Adipose - Acetaminophen (Hydrophilic)



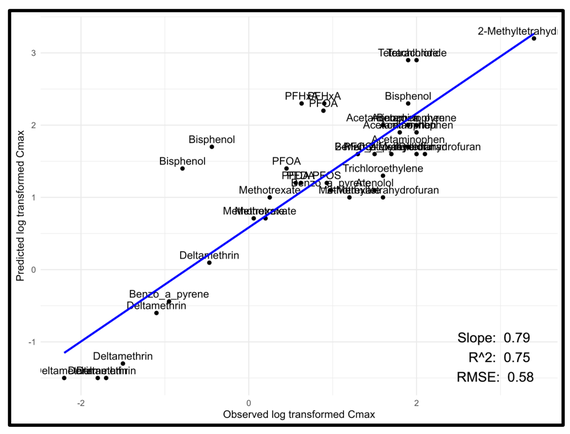
Kpbbb = 0.14, Octanol-Water Partition Coefficient = 0.46
Dosing regimen: daily dose = 14.28 mg/kg, days = 1, doses per day = 1, species = human, route = oral

Adipose - Benzo(a)pyrene (Lipophilic)



Kpbbb = 1, Octanol-Water Partition Coefficient = 6.13
Dosing regimen: daily dose = 10.09 mg/kg, days = 1, doses per day = 1, species = rat, route = IV

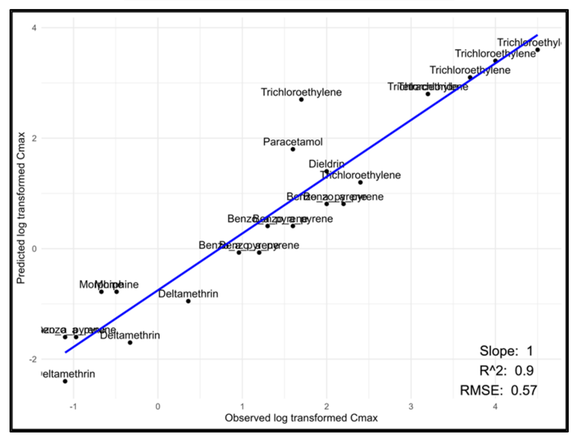
Predicted Vs Observed Brain



The graph compares predicted and observed log Cmax values across 16 different chemicals and 41 unique dosing regimens, each with its corresponding concentration-time profile.

Observed data were derived from multiple studies sourced from literature and the CvT database [6] for oral and intravenous routes.

Predicted Vs Observed Adipose



The graph compares predicted and observed log Cmax values across 7 different chemicals and 23 unique dosing regimens, each with its corresponding concentration-time profile.

Observed data were derived from multiple studies sourced from literature and the CvT database [6] for oral and intravenous routes.

Result

- For acetaminophen, the complex model showed slightly superior performance. However, both simple and complex models provided comparable estimates of experimental Cmax.
- The Cmax values predicted by the complex model for the brain compartment were within 2-fold of the experimental data measurements, as seen in the example hydrophilic acetaminophen (predicted Cmax = 54.01, observed Cmax = 74.03) and lipophilic benzo(a)pyrene (predicted Cmax = 11.21, observed Cmax = 9.59).
- The prediction results, compared with available pharmacokinetic time-series data derived from literature sources and the CvT [6] database, showed overall low disparity between predicted and observed data.
  - For the complex model's Brain compartment, an R-squared (R^2) of 0.75 demonstrated good correlation between predicted and observed and a root mean square error (RMSE) of 0.58 indicated moderate prediction error.
  - The complex model's Adipose compartment displayed strong correlation (R^2 = 0.9) and moderate prediction error (RMSE = 0.57).

Conclusion

- By expanding the existing open-source PBPK modeling approach, this work can refine the quantification of chemical distribution in specific toxicologically relevant body compartments for humans and rats.
- The alignment between the model predictions and predictions from a commercial model and experimental data indicates the robustness of the expanded httk models and their applicability in various aspects of drug development and toxicity research.
- Separating the model outputs based on the hydrophilic and lipophilic properties of compounds enables a more mechanistic understanding of chemical disposition within these body compartments.
- The expanded httk model provides the potential to improve prediction of brain distribution of chemicals. The complex model makes it possible to simulate chemical permeability across the blood-brain barrier.
- Further improvement in the RMSE values for the brain model could potentially be achieved by exploring the role of transporters present on the blood-brain barrier that are not specifically accounted for in this model.

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Acknowledgments

- This project was supported by the Intramural Research Program (ES# 103386) at the National Institute of Environmental Health Sciences, National Institutes of Health under contract HHSN273201500010C. JPS was supported by EPA grant RD840027. We thank Catherine Sprankle, Inotiv, for editorial input.
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