National Institute of Environmental Health Sciences
Division of Translational Toxicology

Expanding PBPK Modeling to Predict Chemical Distribution in Brain and Adipose Tissues

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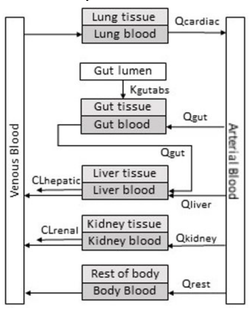
Introduction

- Physiologically based pharmacokinetic (PBPK) models represent absorption, distribution, metabolism, and excretion (ADME) processes to help predict concentrations of chemicals in relevant tissues.
- These models are based on mathematical representations that combine chemical and physiological data using systems of ordinary differential equations.
- Here we build upon the existing generic PBPK model included in the U.S. Environmental Protection Agency's (EPA's) httk package (version 2.2.2) [1] to estimate chemical concentrations in brain and adipose compartments of the body. The httk R package is open-source and can accommodate integration of new models.
- The Integrated Chemical Environment (ICE: https://ice.ntp.niehs.nih.gov/) utilizes existing httk R packages in its PBPK and In Vitro to In Vivo Extrapolation (IVIVE) tools to predict chemical distribution. After testing and validation, the new model compartments will be integrated into these ICE tools, allowing users to predict adipose and brain tissue concentrations.

httk PBPK Model



$$\frac{dA_i}{dt} = Q_i\left([C_{art}] - \frac{A_i}{(P_i \cdot V_i)}\right) - C_i \cdot fu \cdot CL_i$$

A_i : amount in tissue i;
Q_i : blood flow to tissue i;
V_i : volume of tissue i;
$[C_{art}]$: concentration in arterial blood;
Cl_i : metabolic clearance in tissue i;
P_i : the tissue to plasma partition coefficient;
fu : fraction of compound unbound in blood

Conclusions & Future Directions

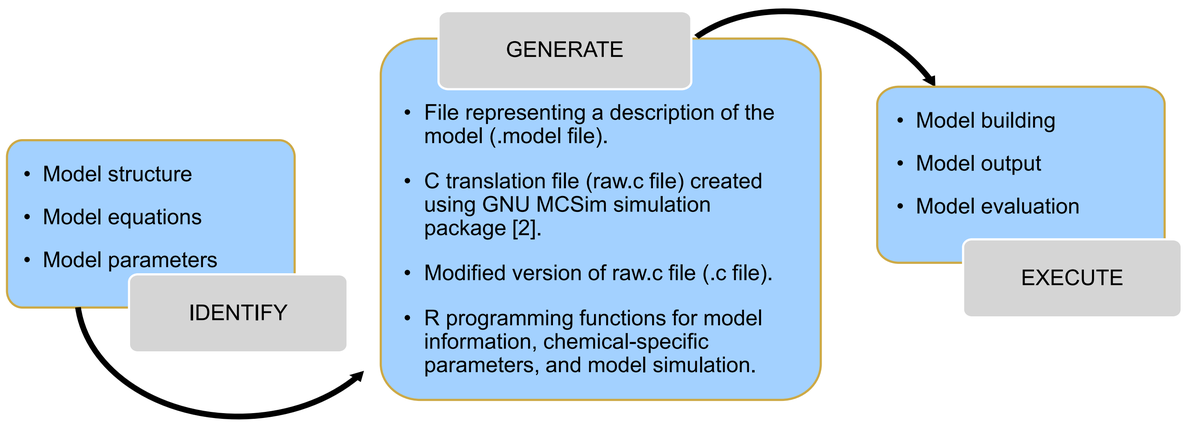
Conclusions:

- 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 human and other species.
- The incorporation of a brain compartment can support the assessment of drug efficacy and potential to induce neurotoxicity. Determining the concentration of chemicals distributed to adipose tissue can provide valuable information on a chemical's likelihood of bioaccumulation.
- The model outputs time series dynamic concentration graphs representing chemical distribution and disposition in these compartments.

Future Directions:

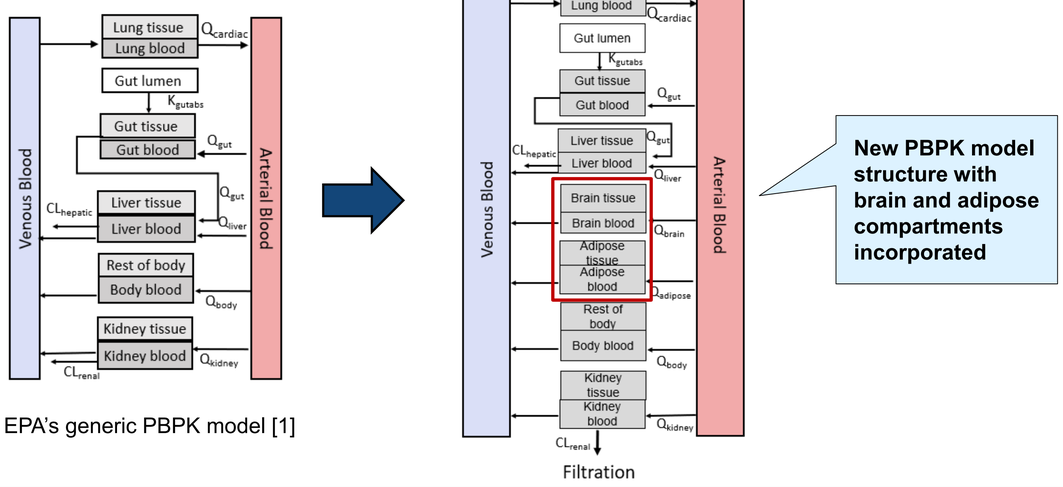
- Perform comparative evaluations based on the output from these models and experimental ADME data identified in the literature.
- Use the same workflow to develop a model with complex brain compartments incorporating the blood-brain barrier, cerebrospinal fluid circulation, and active transporters.
- Incorporate the fully developed and validated models into the httk R package and ICE's PBPK and IVIVE tools.

Workflow: Add New Model to httk Package



PBPK Model Structure

- We built on an existing generalized model from the httk R package that facilitates parameterization with limited data and assumes linear clearance.



EPA's generic PBPK model [1]

Incorporation of Brain Compartment

- To help assess specific toxicological effects such as neurotoxicity, models need to predict chemical distribution to compartments like the brain that have complex and often tissue-specific structural features and may be sensitive to chemical exposures.
- A brain compartment can be simple or complex depending on whether the model incorporates the blood-brain barrier, brain-specific importers and exporters, and drainage via the cerebrospinal fluid.
- We created a simple perfusion-limited brain compartment model based on the generic PBPK model provided by EPA's httk R package.
- We incorporated these physiological parameters specific for brain tissue:

Parameter	Description	Value	Source
Qbrainf	Fraction of cardiac output flowing to the brain tissue	0.125	[1]
Vbrainc	Volume fraction of the brain tissue per kg body weight	0.02	[1,3]

- **Equation for brain:**

$$Q_{brain} = Q_{cardiac} \cdot Q_{brainf} \qquad V_{brain} = V_{brainc} \cdot BW$$

$$\frac{dA_{brain}}{dt} = Q_{brain}\left(\frac{A_{art}}{V_{art}} - \frac{A_{brain}}{V_{brain}} \cdot \frac{R_{blood2plasma} \cdot f_{up}}{K_{brain2pu}}\right)$$

A_{art}: chemical amount in arterial compartment
A_{brain}: chemical amount in brain
BW: body weight
f_{up}: unbound fraction in plasma
$K_{brain2pu}$: brain to plasma partition coefficient
Q_{brain}: blood flow to brain
Q_{brainf}: fraction of blood flow to brain out of total cardiac output
$Q_{cardiac}$: total cardiac output
$R_{blood2plasma}$: blood to plasma concentration ratio
V_{art}: volume of arterial compartment
V_{brain}: brain volume

Incorporation of Adipose Compartment

- As a storage compartment for lipophilic chemicals, adipose tissue affects distribution of a variety of chemicals, particularly persistent organic pollutants, and can act as a source of chronic internal exposure.
- We incorporated these physiological parameters specific for adipose tissue:

Parameter	Description	Value	Source
Qadiposef	Fraction of cardiac output flowing to the adipose tissue	0.05	[4]
Vadiposec	Volume fraction of the adipose tissue per kg body weight	0.21	[1, 4]

- **Equation for adipose**:

$$Q_{adipose} = Q_{cardiac} \cdot Q_{adiposef} \qquad V_{adipose} = V_{adiposec} \cdot BW$$

$$\frac{dA_{adipose}}{dt} = Q_{adipose}\left(\frac{A_{art}}{V_{art}} - \frac{A_{adipose}}{V_{adipose}} \cdot \frac{R_{blood2plasma} \cdot f_{up}}{K_{adipose2pu}}\right)$$

$A_{adipose}$: chemical amount in adipose
A_{art}: chemical amount in arterial compartment
BW: body weight
f_{up}: unbound fraction in plasma
$K_{adipose2pu}$: adiposeto plasma partition coefficient
$Q_{adipose}$: blood flow to adipose
$Q_{adiposef}$: fraction of blood flow to adipose out of total cardiac output
$Q_{cardiac}$: total cardiac output
$R_{blood2plasma}$: blood to plasma concentration ratio
V_{art}: volume of arterial compartment
$V_{adipose}$: adipose volume

PBPK Model Output

- We chose acetaminophen as the test chemical for the brain compartment because it rapidly enters the brain by passive permeability, without the need for a transporter, and there is extensive animal and human data [5].
- We chose bisphenol A as the test chemical for the adipose compartment. Bisphenol A is a lipophilic chemical that accumulates in human tissues, which can contribute to development of health issues like type 2 diabetes [6,7]. Identifying the concentration-time profile of this chemical in adipose tissue provides information on its pharmacokinetic disposition.
- Results of a test of our models with these chemicals are shown below.

Cmax (μM) and Tmax (hours) in the Compartments of Interest

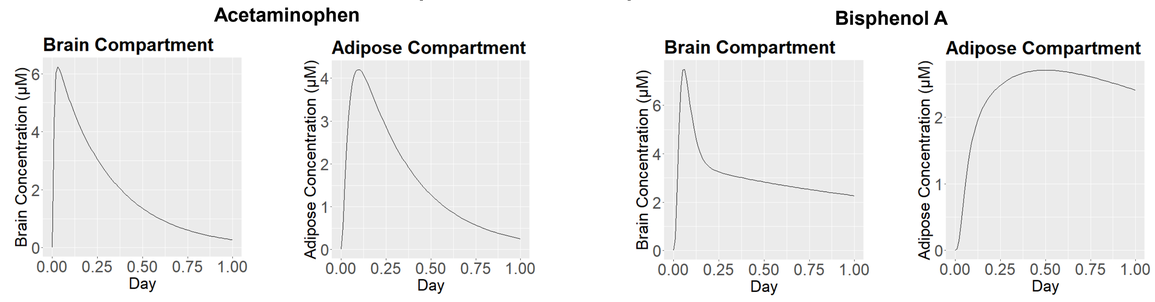
Model	Chemical	Cmax, μM			Tmax, Hours		
		Rest of Body*	Brain	Adipose	Rest of Body*	Brain	Adipose
Solve_pbtk	Acetaminophen	5.1	-	-	1.5	-	-
Brain + Adipose	Acetaminophen	5.5	6.1	4.2	1.5	1	2.5
Solve_pbtk	Bisphenol A	4	-	-	4	-	-
Brain + Adipose	Bisphenol A	4.5	7.4	2.7	4	1.5	12

Cmax: maximum concentration; Tmax: time to Cmax
* "Rest of Body" for Brain and Adipose models excludes brain and adipose tissues.

Dosing Regimen

Daily Dose = 1 mg/kg
Days = 1
Doses Per Day = 1
Species = Human

Output from Brain + Adipose Model



- Expected accumulation in adipose compartments was observed for bisphenol A but not for acetaminophen. Literature findings tends to support these predictions for acetaminophen and bisphenol A [5, 8].
- Compared to the generic pbtk model in the httk package, the new model was able to predict the dynamic distribution to brain and adipose compartments. This helps create a foundation for further refined pharmacokinetic modeling.

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