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Generic Pharmacokinetic Models for Mother-to-Offspring Transfer of Chemicals

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Office of Research and Development
Center for Public Health and Environmental Assessment

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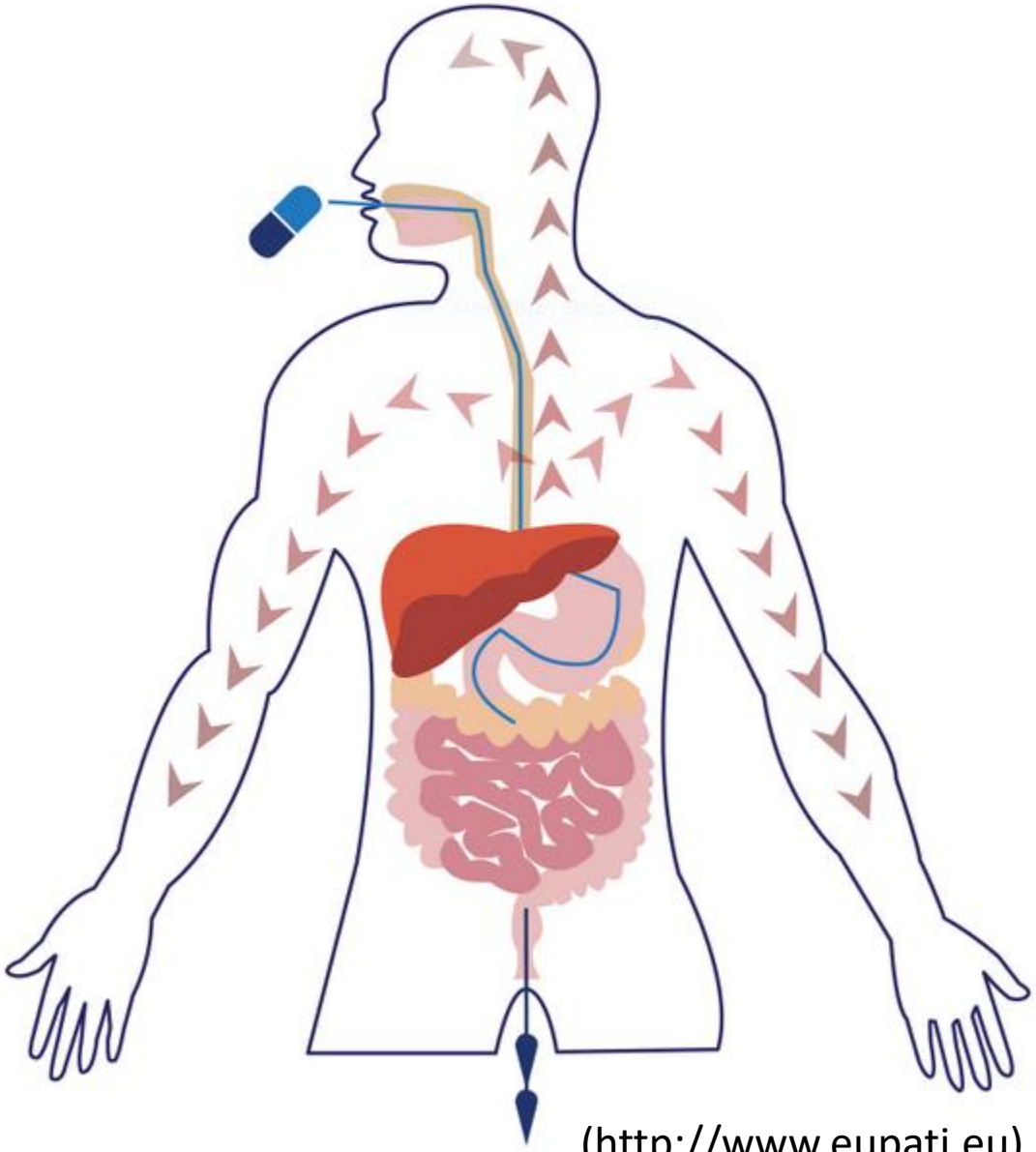
Outline

- Overview of PK Modeling Concepts
- Pregnancy and Gestation PK Modeling
- Generic PK Model for Mother-to-Offspring Transfer of LPECs
- Generic Human PBPK Model for Human Pregnancy and Gestation
- Summary

What is Pharmacokinetics?

- Branch of pharmacology that deals with **fate and transport** of a drug (or other substance) within an organism.
- Accounts for **absorption**, **distribution**, **metabolism**, and **excretion** (**ADME**).
- *What the body does to the substance*.
- Different from **pharmacodynamics** (*what the substance does to the body*).



(http://www.eupati.eu)

What is a Pharmacokinetic Model?

- A **quantitative statement** of a **set of hypotheses** regarding ADME.
- Typically expressed as a system of ODEs* that describe the amounts of a substance in various "compartments" of an animal's body.

General ODE Form:

$$\frac{\mathrm{d}}{\mathrm{d}t}[\text{Amount}] = [\text{Rate In}] - [\text{Rate Out}]$$

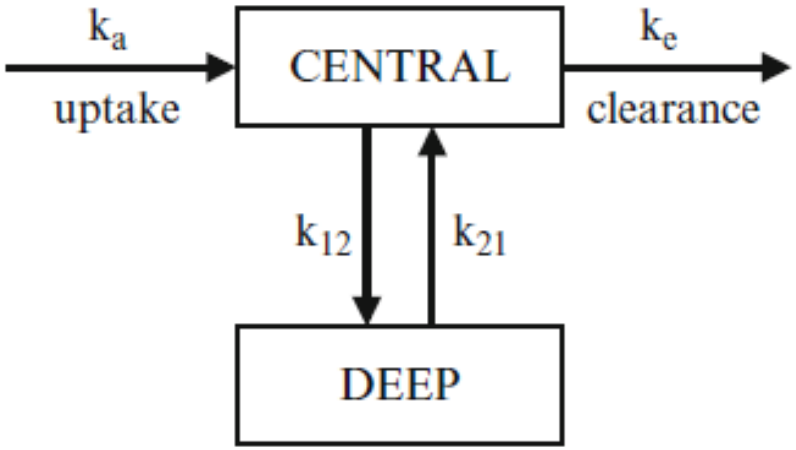
- There are <u>two major classes</u> of PK† models …

*ODE = ordinary differential equation

†PK = pharmacokinetic

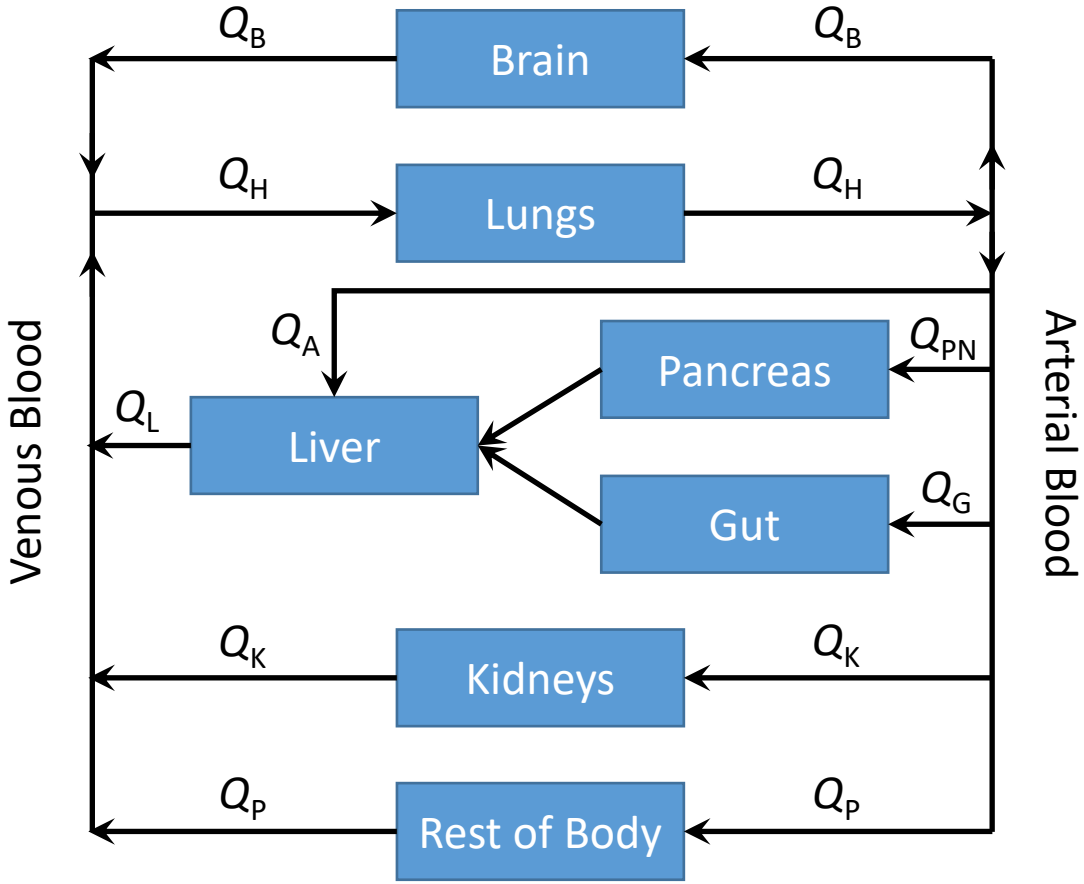
Two Classes of PK Models

Classical PK Models



(Campbell et al., 2012)

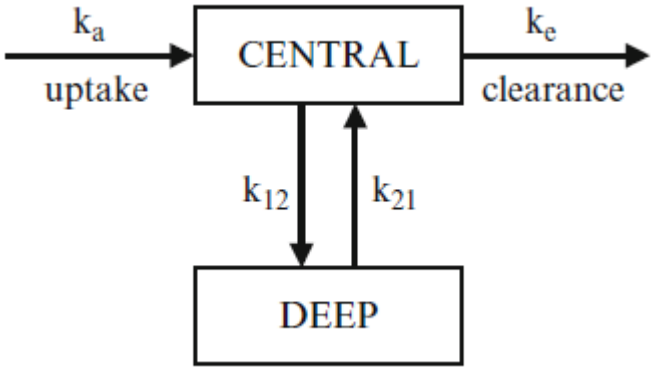
PBPK* Models



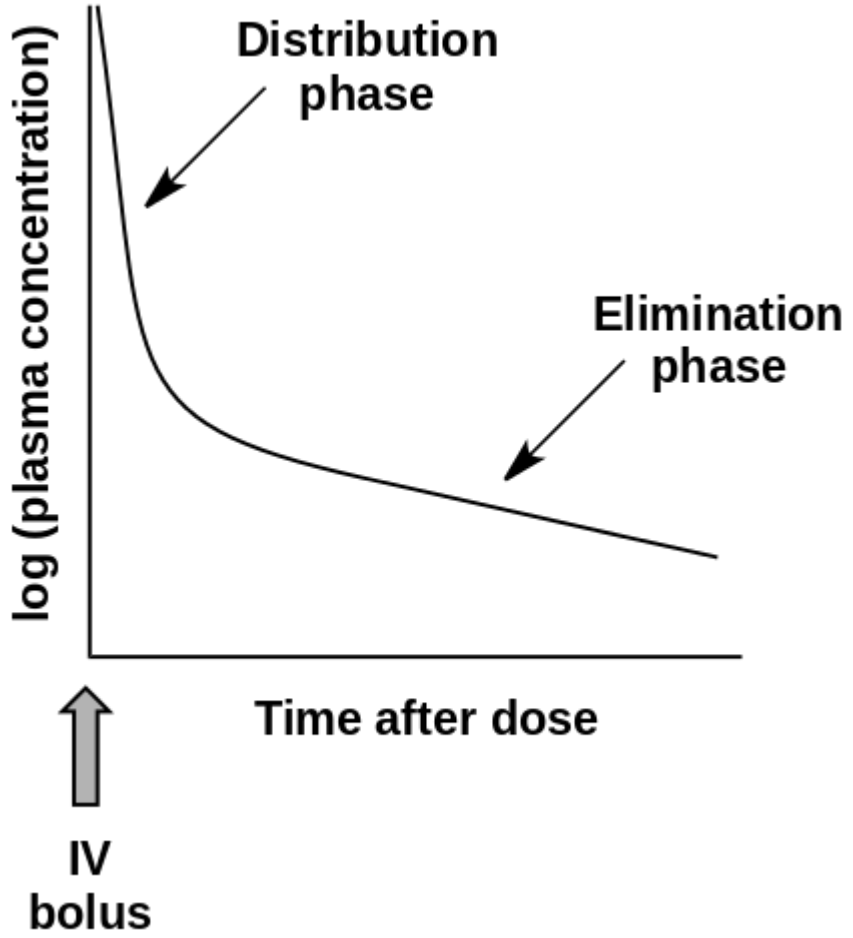
*PBPK = physiologically based pharmacokinetic

Classical PK Modeling

- **Empirical** approach
- **Number of compartments** is selected to obtain a good **fit** to **available data**.
- **Compartments** generally do not correspond to **distinct organs or tissues**.

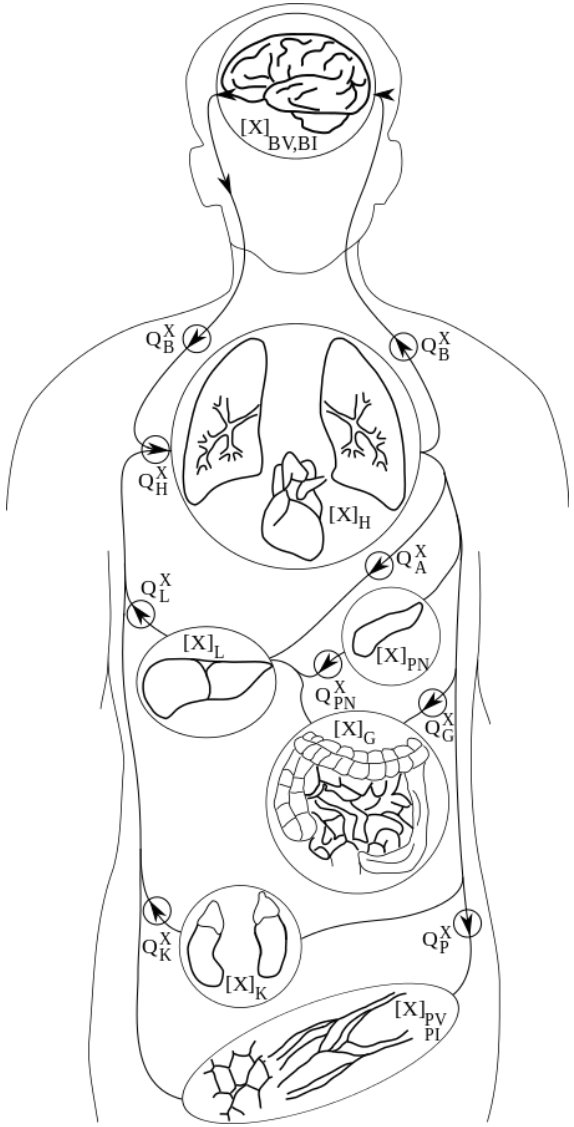


(Campbell et al., 2012)



(Wikimedia Commons)

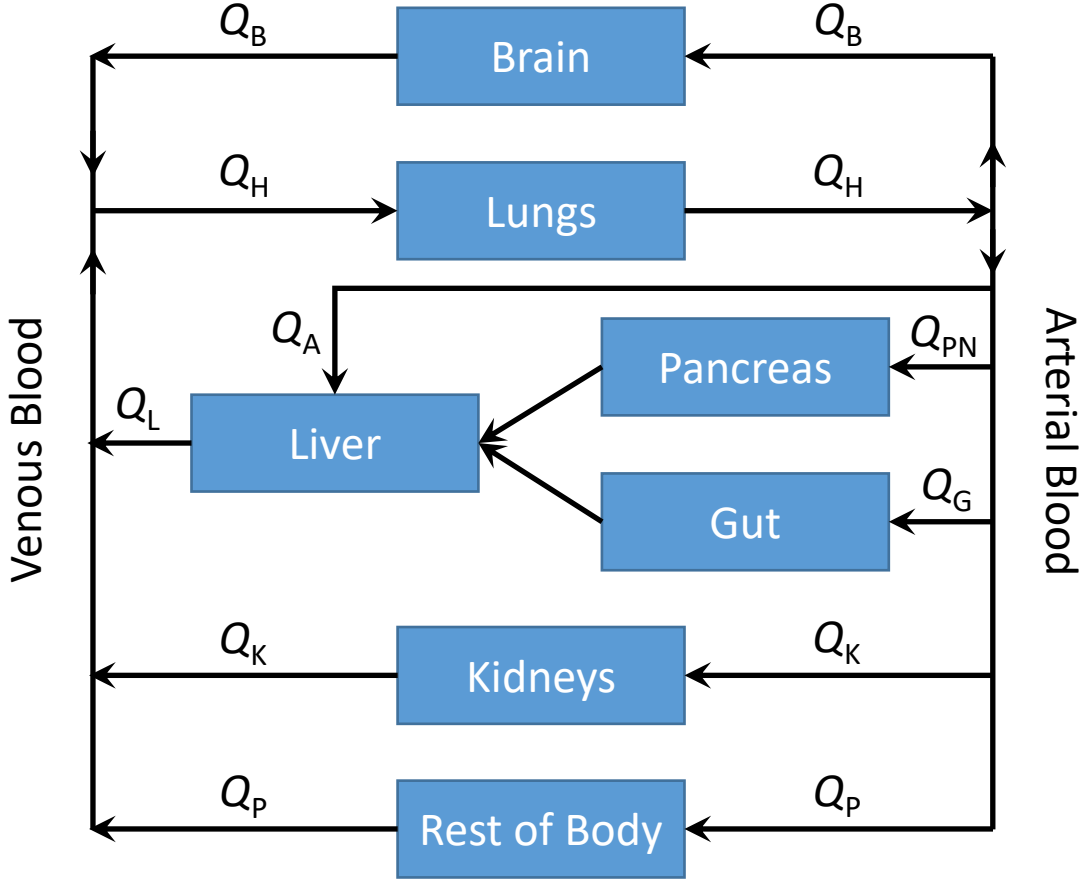
PBPK (or PBTK*) Modeling



(Wikimedia Commons)

Chemical engineering applied to a **biological organism**

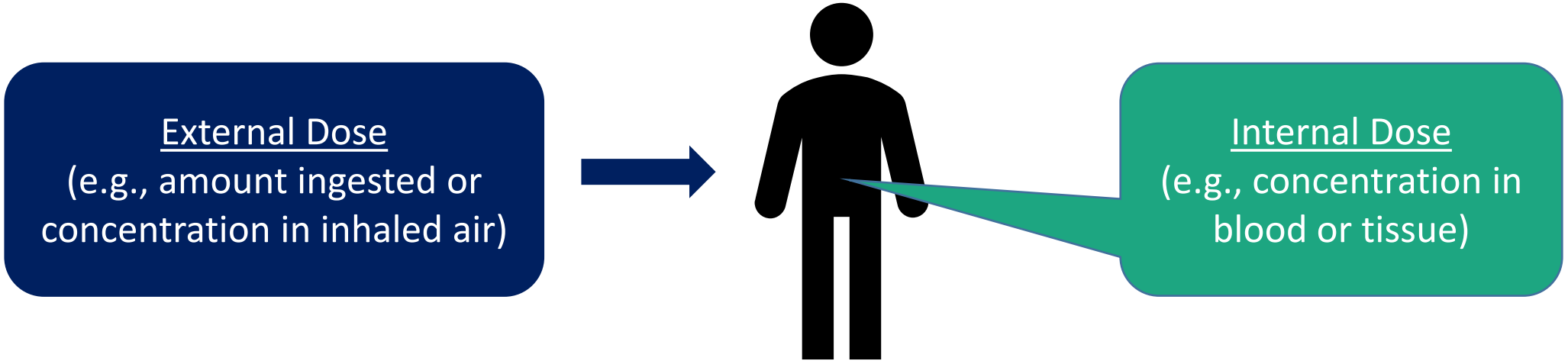
Model **parameters** are based on **anatomy**, **physiology**, and **biochemical properties**.



*PBTK = physiologically based toxicokinetic

Dosimetry

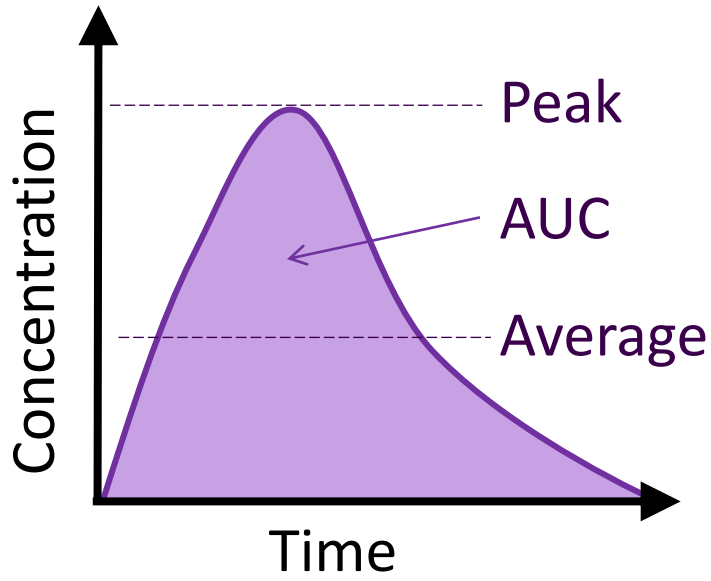
- Both PBPK and classical PK models allow for conversions between **external** and **internal** measures of dose.



- Motivated by the expectation that **observed effects** are more directly related to **target tissue dose** than **administered (or exposure) dose**.

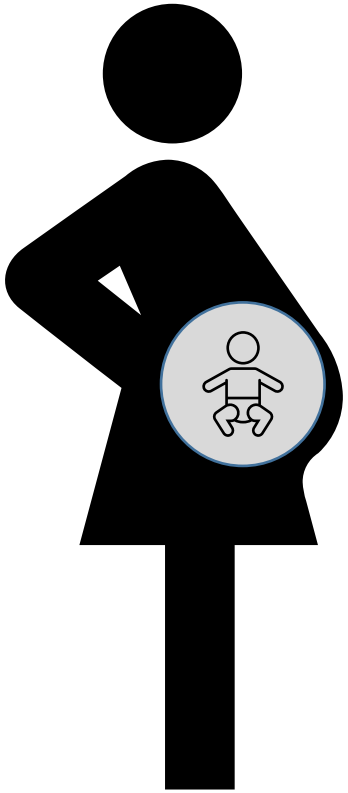
Internal Dose Metrics

- **Internal dose metrics** quantify internal exposure.
- For a model that can estimate internal concentrations (e.g., in blood) vs. time, the following dose metrics might be useful.
  - **Area-under-the-concentration-curve (AUC)** reflects cumulative exposure
  - **Average concentration** reflects cumulative exposure over a given time period
  - **Peak concentration** reflects short-term exposure intensity



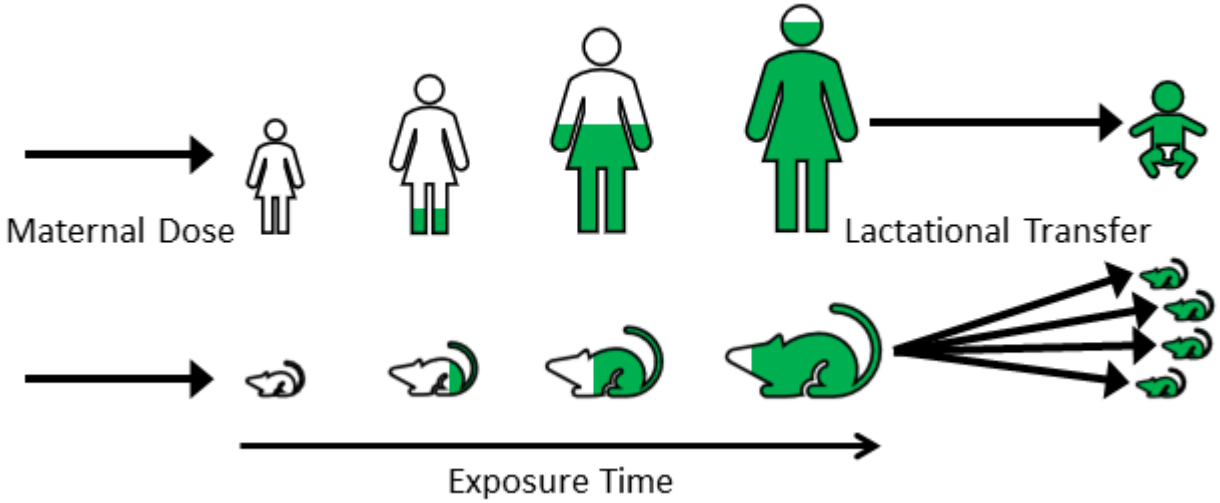
Pregnancy and Gestation PK Modeling

- PK models can describe **ADME** in a **pregnant mother** and her **gestating embryo/fetus**.
- **Transplacental transfer** mechanisms can be represented in the models.
- Some pregnancy PK models examine a “snapshot” in time (e.g., Lumen et al., [2013] considered “near-term” pregnancy).
- However, it may be important to account for relatively **rapid and substantial changes** in parameters that describe **anatomical** and **physiological** quantities.

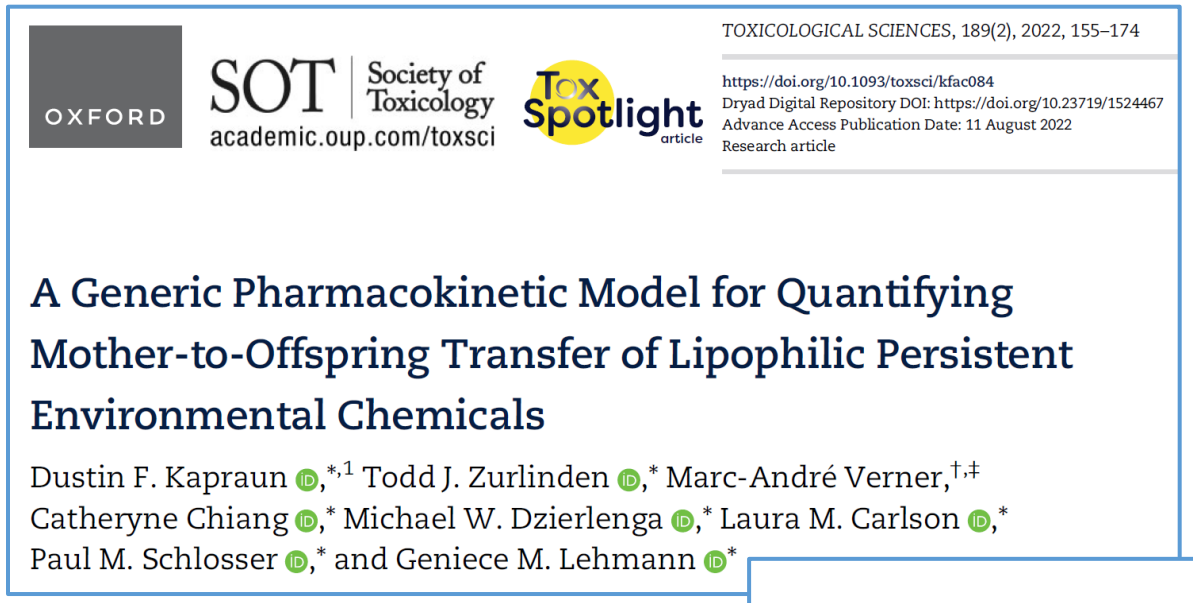


Postnatal PK Modeling

- PK models can describe **ADME** in a **mother** and her **infant(s)**, including **lactational transfer**.
- It's important to account for changes in **anatomical** and **physiological** quantities.
- For persistent chemicals, exposures that occur <u>before</u> the postnatal period can have an impact.



“Generic” PK Models for Mother-to-Offspring Transfer



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A Generic Pharmacokinetic Model for Quantifying Mother-to-Offspring Transfer of Lipophilic Persistent Environmental Chemicals

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“Model A”

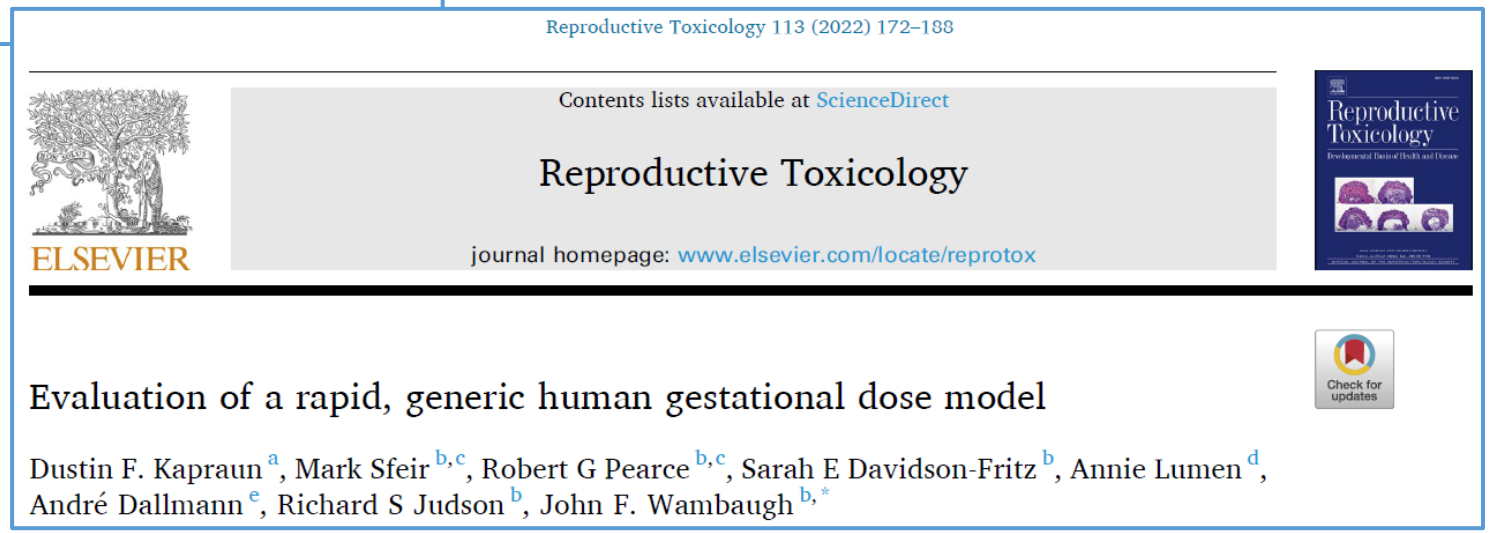
“Pseudo-Classical” PK Model

([Kapraun et al., 2022a](#))

“Model B”

PBTK Model

([Kapraun et al., 2022b](#))



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Evaluation of a rapid, generic human gestational dose model

Dustin F. Kapraun [a], Mark Sfeir [b,c], Robert G Pearce [b,c], Sarah E Davidson-Fritz [b], Annie Lumen [d], André Dallmann [e], Richard S Judson [b], John F. Wambaugh [b,*]

Acknowledgments (Model A)

"A Generic PK Model for Mother-to-Offspring Transfer of Lipophilic Persistent Environmental Chemicals"

Todd Zurlinden (U.S. EPA)

Marc-André Verner (U. Montreal)

Catheryne Chiang (U.S. EPA)

Michael Dzierlenga (U.S. EPA)

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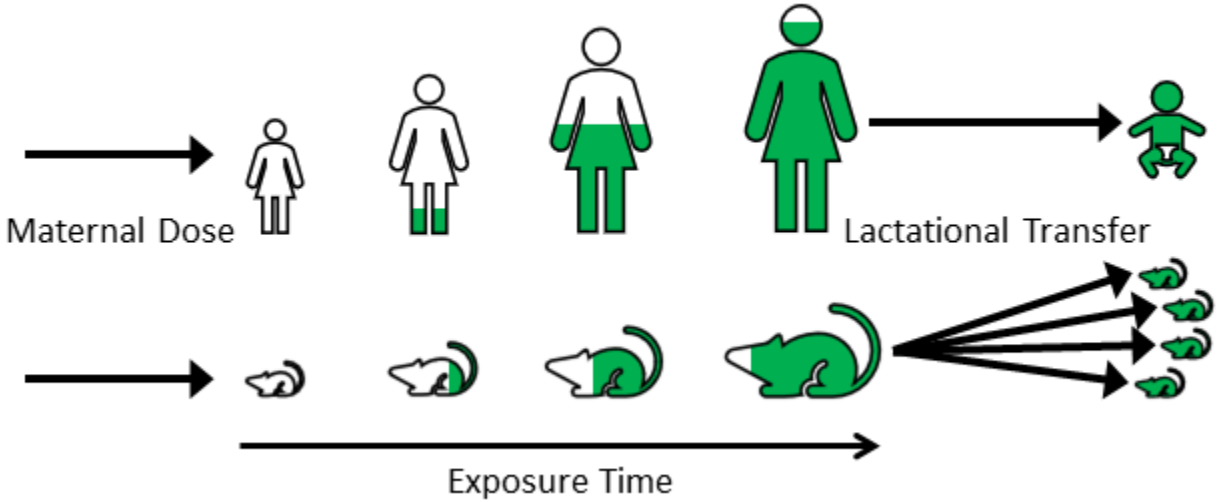
Geniece Lehmann (U.S. EPA)

Motivation

- LPECs* may accumulate in a woman's body (in body lipids) over the course of many years.
- They may be transferred to her offspring during pregnancy and nursing.



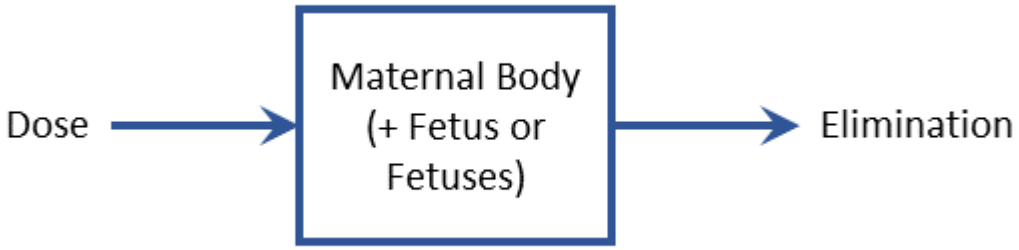
- A nursing infant may be exposed at a rate (mg/kg/d) that exceeds the exposure or dose (mg/kg/d) experienced by the mother.
- Therefore, dose-response analyses based on <u>maternal</u> **dose metrics** *may not be adequate* for assessing risks to **offspring**.

*LPEC = lipophilic persistent environmental chemical

PK Model for Mother-to-Offspring Transfer of LPECs

Model A

Prior to and during pregnancy:

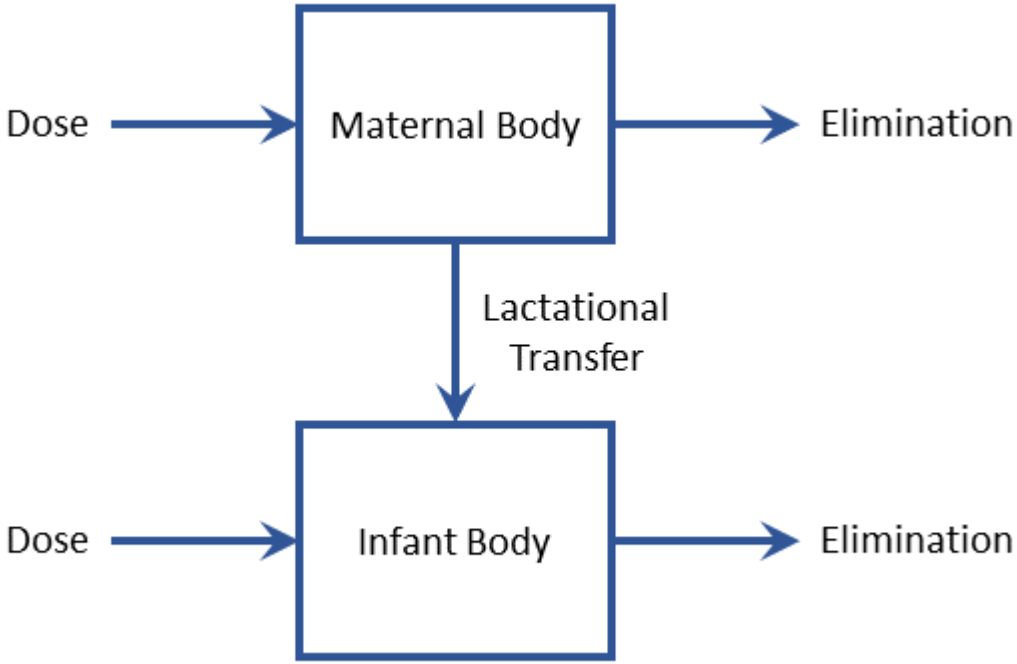


Key Assumptions:

- Elimination rate is proportional to amount of chemical in the body.
- Ratio of concentrations in mother and in utero fetuses is constant.

Some model parameters (e.g., body masses) are **time-dependent**.

During lactation and nursing:



Key Assumptions:

- Elimination rate is proportional to amount of chemical in the body.
- Chemical is transferred through milk lipids.

Model Needs & Assumptions

- User supplies **exposure scenario details**:

Required	Optional (default values available)
Animal **species** (mouse, rat, or human)	Duration of pregnancy/gestation
Chemical elimination **half-life** in the animal	Duration of lactation/nursing period
Dose level	Body mass vs. time for mother
Dose type (direct or via food*)	Lipid fraction for maternal body and milk
Dose regimen (start and end times)	Litter size, body mass vs. time, and milk ingestion rate vs. time for offspring

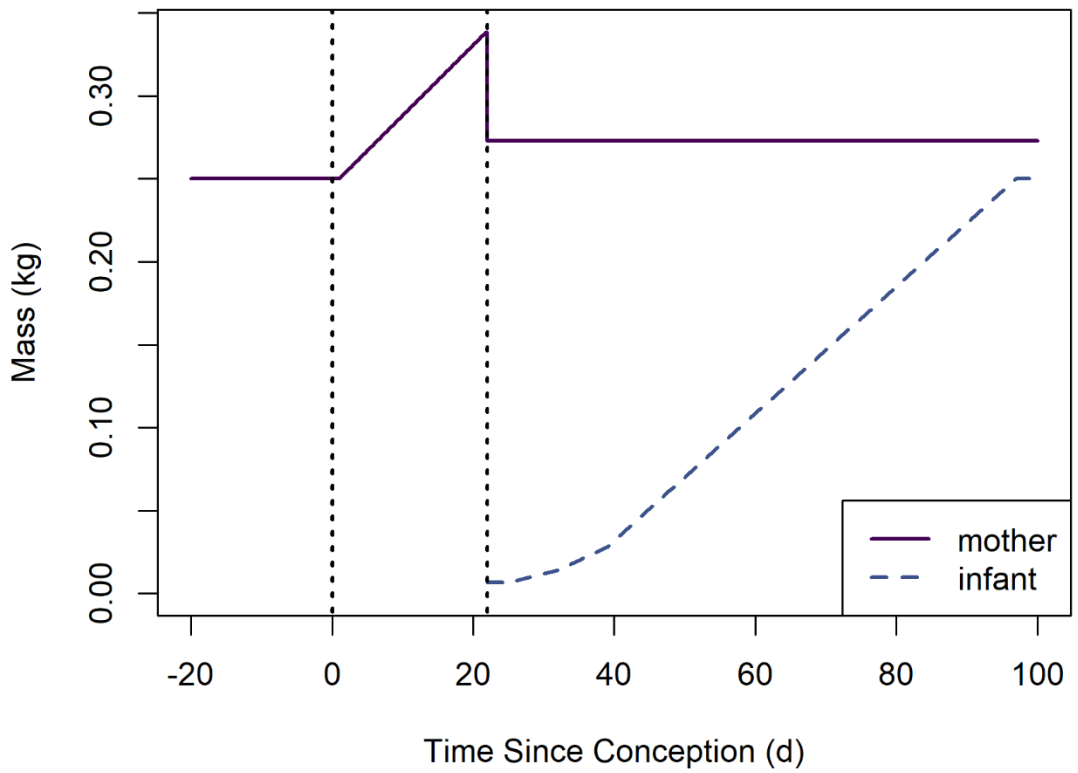
- **Mass is conserved** (e.g., at birth).
- **Piecewise linear** functions of time describe **body masses** and **milk ingestion rates**. These are **continuous**, except at birth and weaning.

*For "direct" doses, dose levels are rates (mg/kg/d) delivered to mother and/or offspring. For "food" doses, dose levels are concentrations (mg/kg) in food and food consumption rates are estimated based on body mass. In either case, an absorption fraction parameter can be provided.

Piecewise Linear Functions:
Body Mass

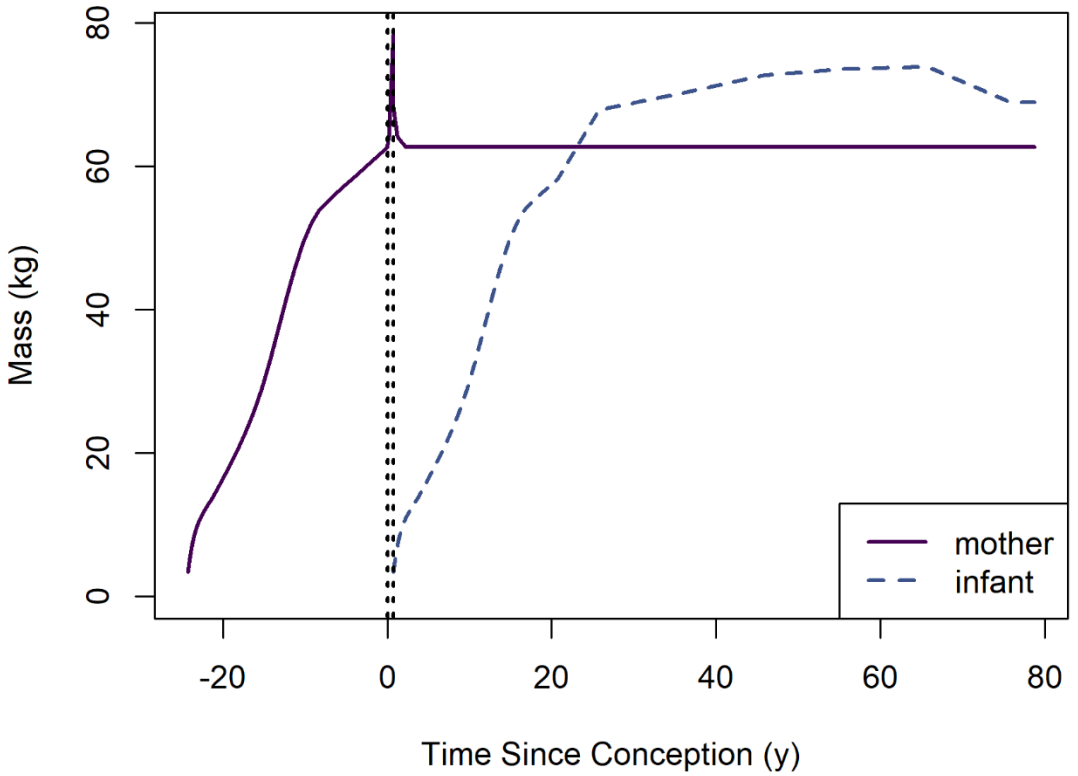
Model A

Rat



Based on data from U.S. EPA (1988) and Lehmann et al. (2014)

Human



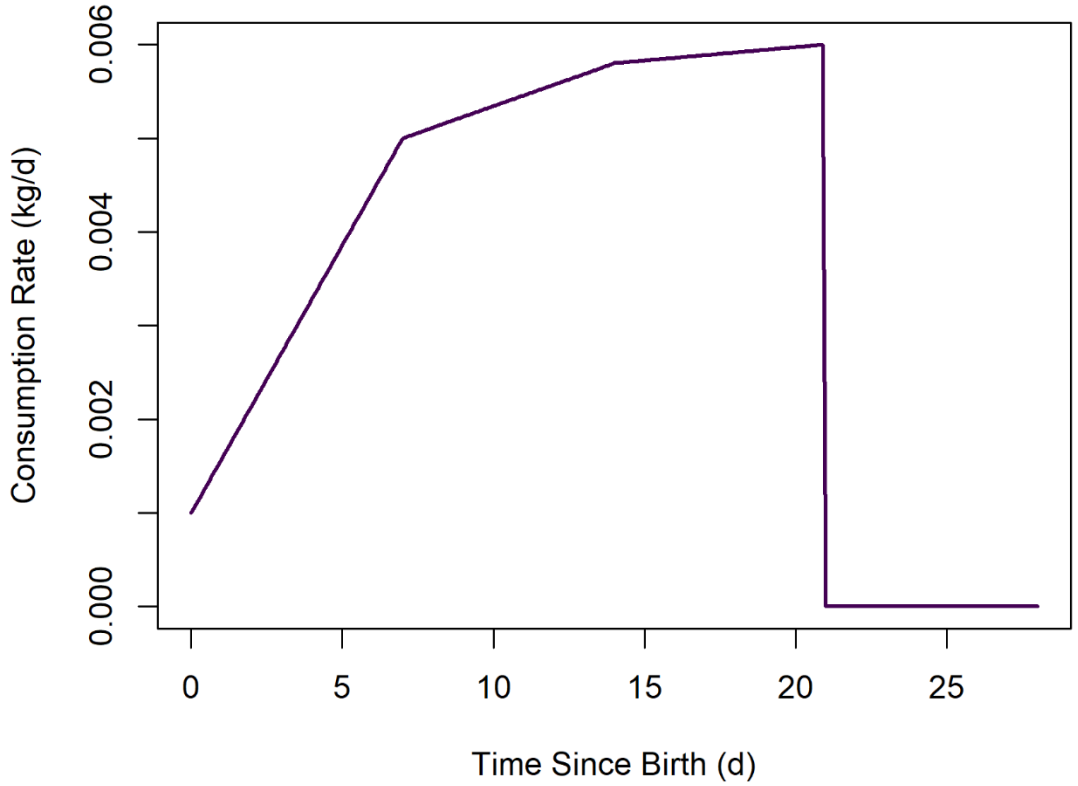
Based on data from Kuczmarski et al. (2002), U.S. EPA (2011a), Carmichael et al. (1997), Portier et al. (2007), Thorsdottir and Bergisdottir (1998), and Dewey et al. (1993).

Dashed vertical lines in each panel indicate offspring conception (left) and birth (right).

Piecewise Linear Functions:
Milk Consumption Rate

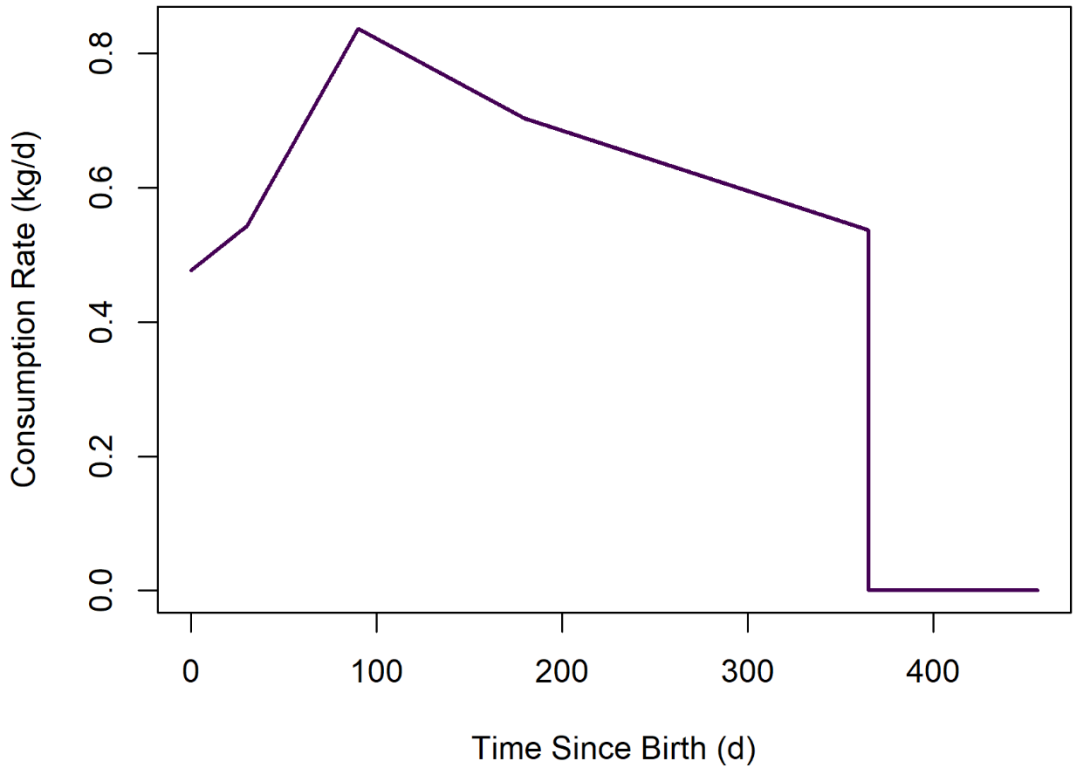
Model A

Rat



Based on data from Lehmann et al. (2014)

Human

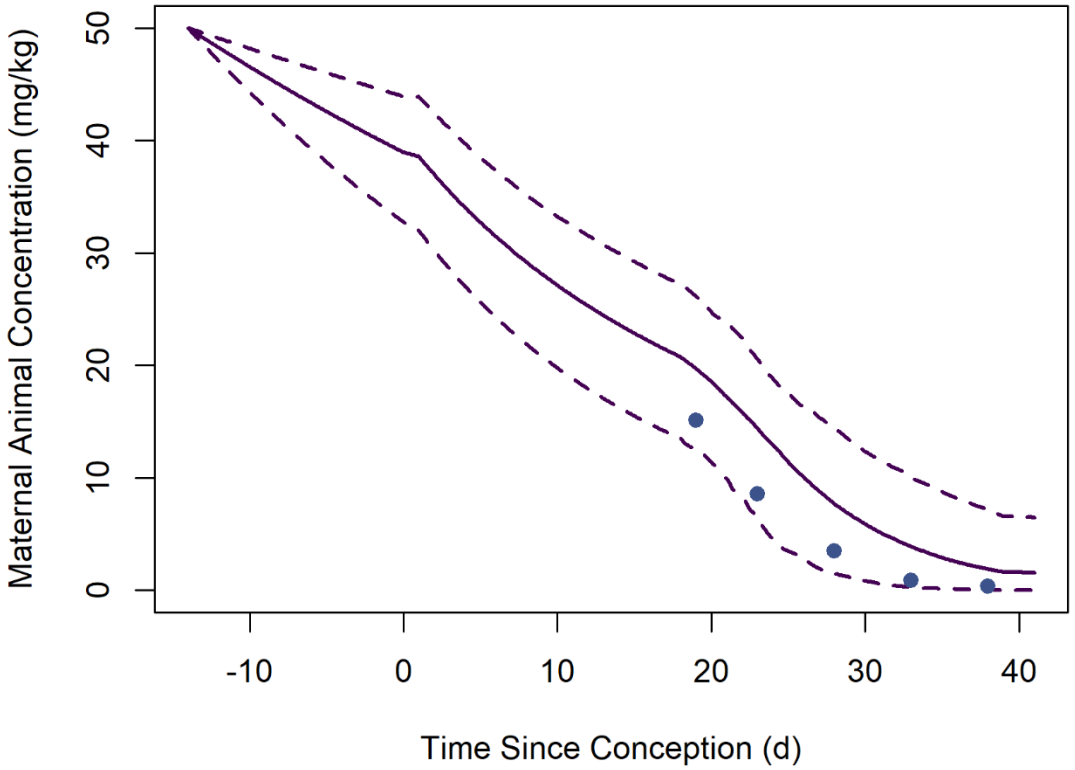


Based on data from U.S. EPA (2011a)

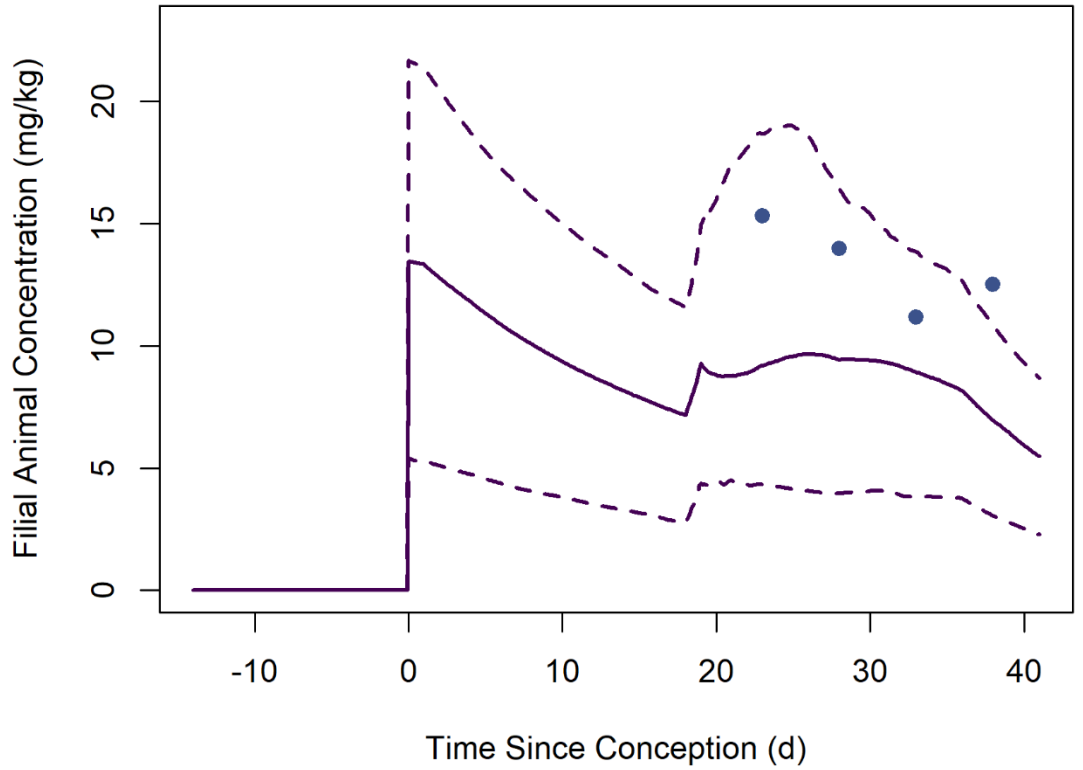
Model Evaluation Results

Model A

Mother



Offspring



Whole body concentrations (mg/kg) of **PCB 153** in mouse dams and fetuses **observed** (solid circles) by Vodicnik and Lech (1980) and **estimated** (lines) based on MC model simulations of that study. The solid line represents the median predicted concentrations from the MC simulations, whereas the dashed lines represent the lower and upper bounds of a 95% credible interval for the predicted concentrations.

HED Example

To compute HEDs* for the rat HCB† dosing regimen described by Nakashima et al. (1997), we used a half-life of 6 y for HCB in humans (To-Figueras et al., 2000).

Dose Metric (Offspring)	Dose Metric Value (mg/kg)	HED (mg/kg/d)
Peak concentration during gestation and nursing	0.186	3.97×10^{-5}
Average concentration during gestation and nursing	0.070	2.91×10^{-5}
Average concentration during gestation	0.018	1.73×10^{-5}
Average concentration during nursing	0.142	4.13×10^{-5}

*HED = human equivalent dose

†HCB = hexachlorobenzene

HED Example

We can compare HEDs for the rat study (Nakashima et al., 1997) calculated using our PK model to one that might be calculated using an **alternative dosimetry method** based on allometric scaling (U.S. EPA, 2011b).

- **Dose applied** to **rat dams**: 0.1 mg per kg of food
- **Converting** based on food consumption rate: 0.00870 mg/kg/d
- **Allometric scaling**:
  - Rat dam mass (Nakashima et al., 1997): 0.247 kg
  - Pregnant woman mass (U.S. EPA, 2011a): 75 kg
  - Scaling factor: $(0.247 / 75)^{1/4} = 0.240$
- **HED:** $0.00870 \times 0.240 = \mathbf{2 \times 10^{-3}}$ **mg/kg/d**
- **This value is considerably larger than the HEDs we computed using our PK model, which accounts for bioaccumulation, mother-to-offspring transfer, and dosimetry of LPECs.**

HED (mg/kg/d)
3.97×10^{-5}
2.91×10^{-5}
1.73×10^{-5}
4.13×10^{-5}

Summary (Model A)

- We developed a generic **PK model** that quantifies **transfer** of **LPECs** from mother to offspring during **gestation** and **nursing**.
  - ➢ The only required chemical-specific parameter is **half-life** in animal species of interest.
- We **evaluated** our **PK model** using **PK data** from developmental studies.
- We **demonstrated** how the PK model can be used to **calculate HEDs** and **compared** results with those generated using an **alternative HED** calculation method.
- **HEDs** calculated using our PK model were about **2 orders of magnitude lower** than those generated using allometric scaling.
- Our PK model can be used to calculate internal dose metrics for offspring and corresponding HEDs and thus informs assessment of developmental toxicity risks associated with LPECs.

Acknowledgments (Model B)

"Evaluation of a Rapid, Generic Human Gestational Dose Model"

Mark Sfeir (ORISE, U.S. EPA)

Robert Pearce (ORISE, U.S. EPA)

Sarah Davidson (U.S. EPA)

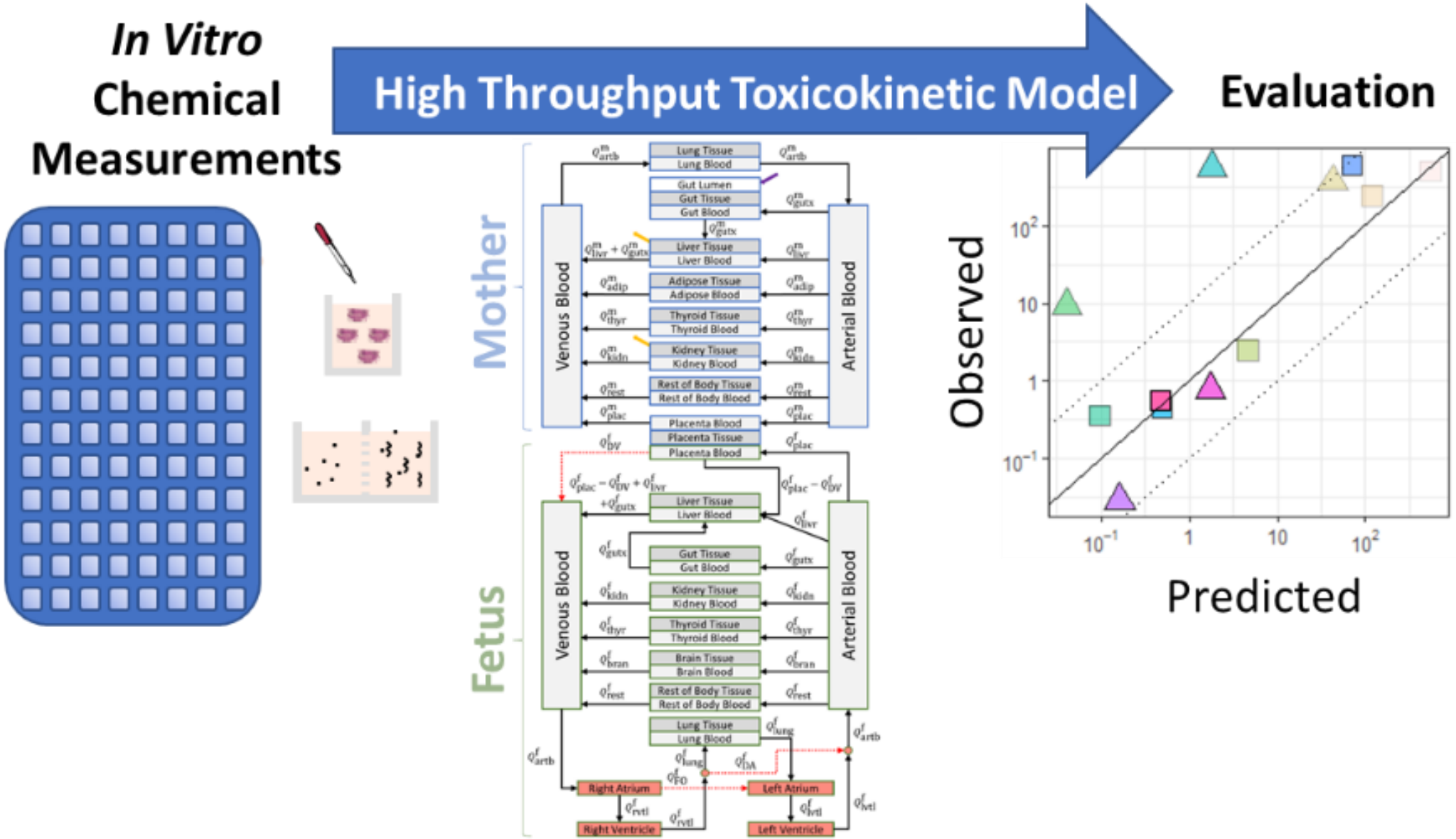
Annie Lumen (U.S. FDA)

André Dallmann (Bayer)

Richard Judson (U.S. EPA)

John Wambaugh (U.S. EPA)

Graphical Abstract (Model B)



Extension of R Package "httk" (Model B)

1-Comp 3-Comp PBTK Maternal/Fetal PBTK

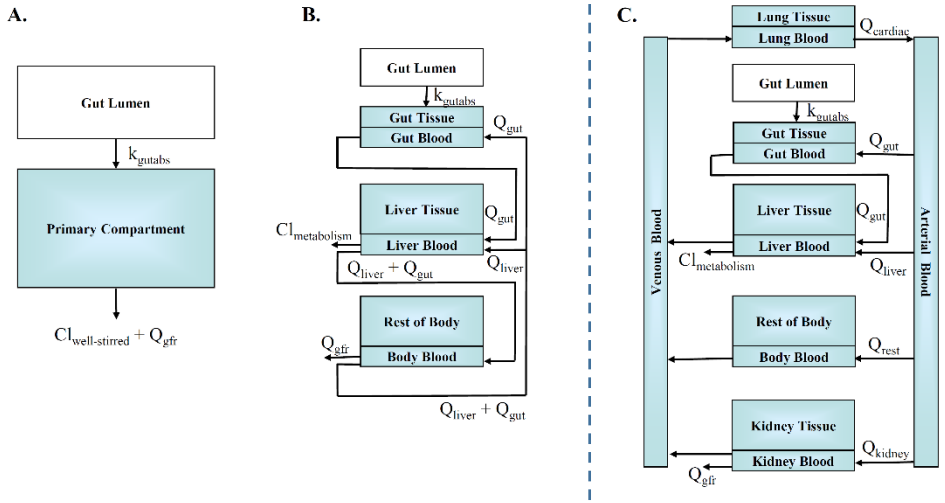
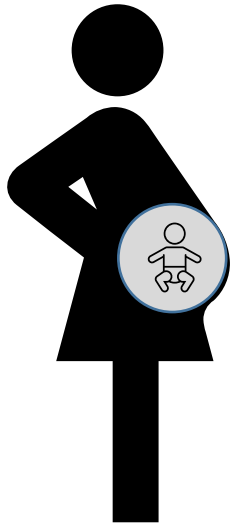


Figure 1: Models (A) 1compartment, (B) 3compartment, and (C) pbtk. In order to preserve mass-balance, Q_{rest} is defined as the difference between $Q_{cardiac}$ and the flow to the liver, kidney, and gut. Variable names are defined in Table 1.

(Pearce et al., 2017a)



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RESEARCH ARTICLE

Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation

Dustin F. Kapraun[1]*, John F. Wambaugh[2], R. Woodrow Setzer[2], Richard S. Judson[2]

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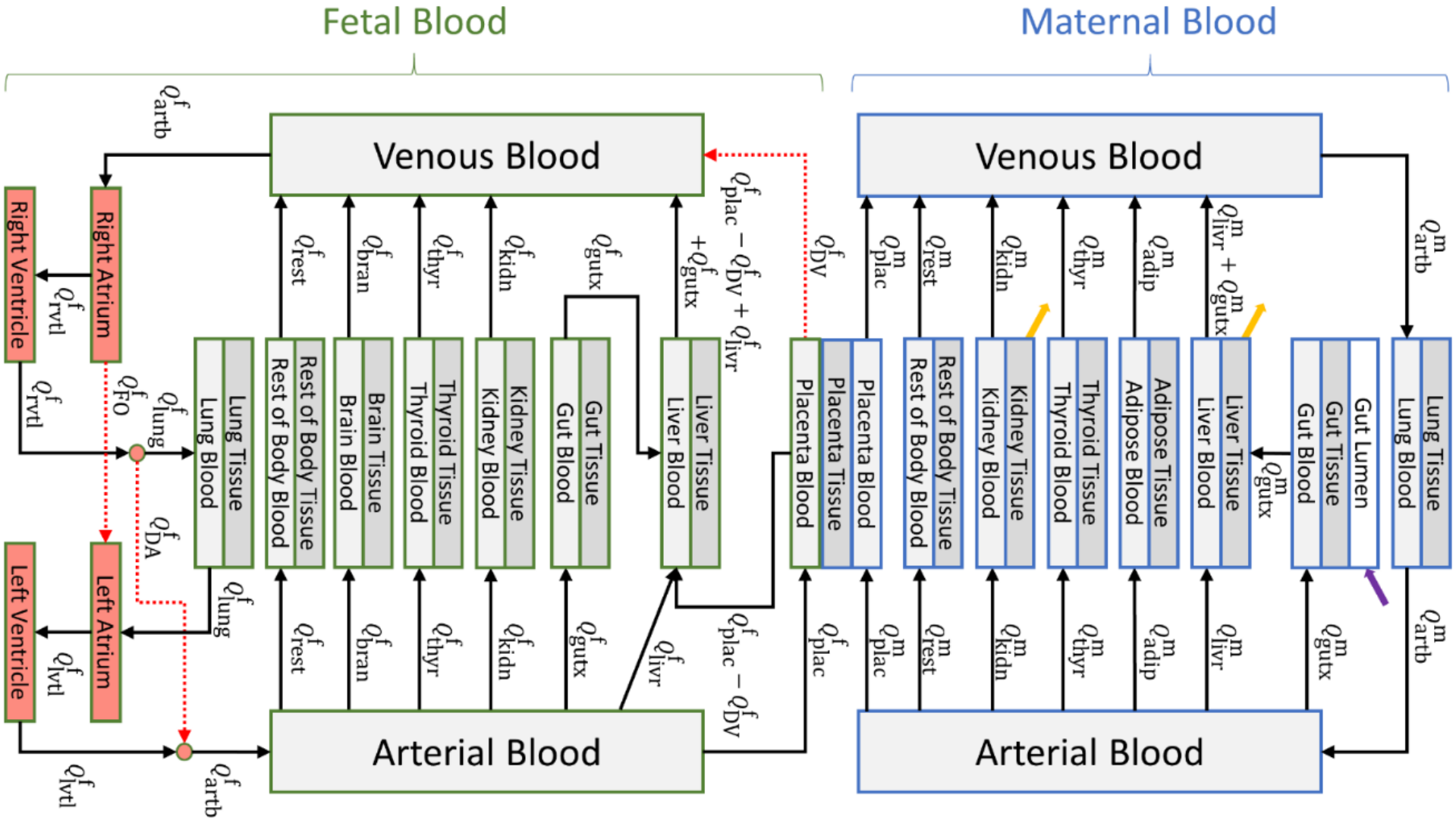
(Kapraun et al., 2019)

HTTK Maternal/Fetal PBTK Model

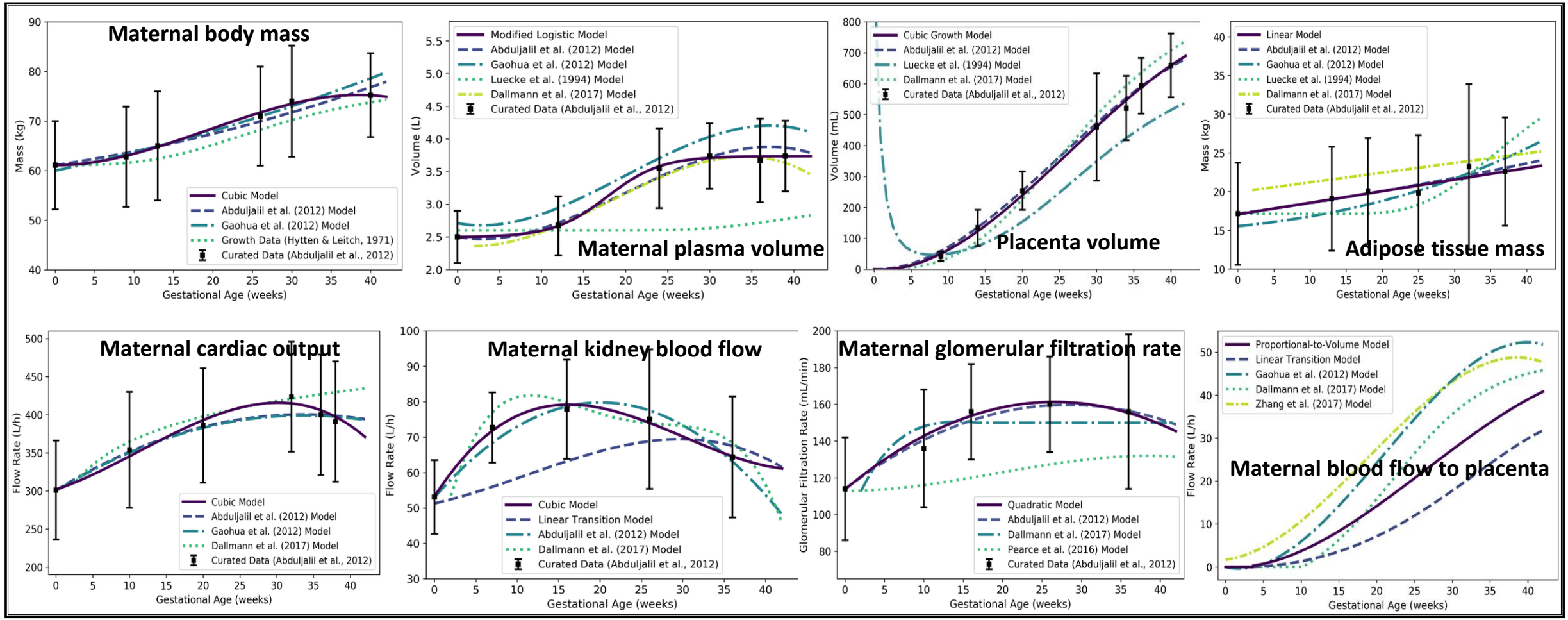
Model B



(Kapraun et al., 2022b)

Time-Varying Maternal Parameters

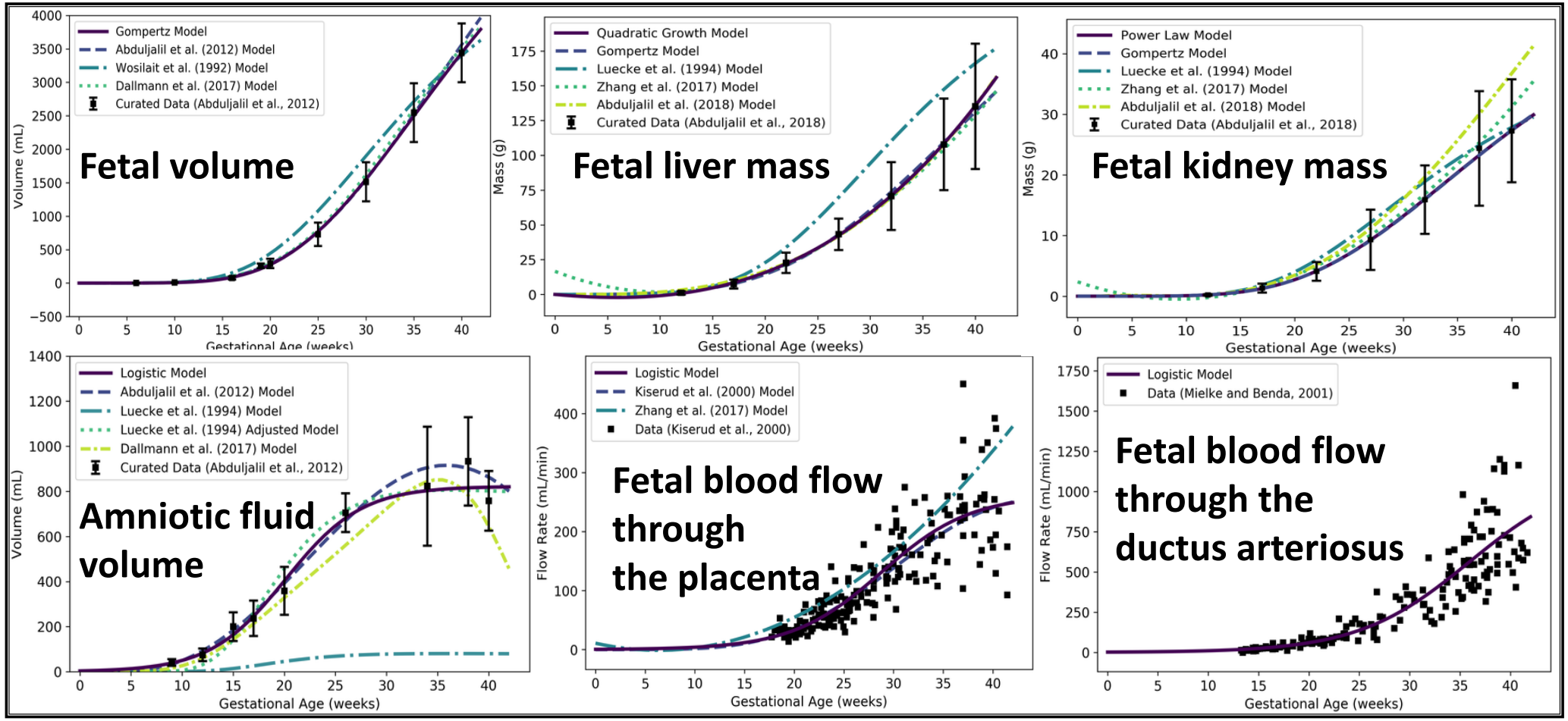
Model B



(Kapraun et al., 2019)

Time-Varying Fetal Parameters

Model B



([Kapraun et al., 2019])

HTTK Maternal/Fetal PBTK Model

Model B

Features Included:

- Description of fetal physiology and the evolving fetal circulatory system in pregnancy PBPK models
- Temporal changes in maternal and fetal physiological parameters (e.g., body mass, compartment volumes, and blood flow rates) informed by the most current human experimental data available
- Designed to simulate ADME in mother and fetus from 13 weeks gestation to term
- Placental/fetal transfer is described using partition coefficients, which might be sufficient for many chemicals
- Accommodates analysis (IVIVE/forward/reverse dosimetry) for more than 900 chemicals

HTTK Maternal/Fetal PBTK Model

Model B

Features Not Included:

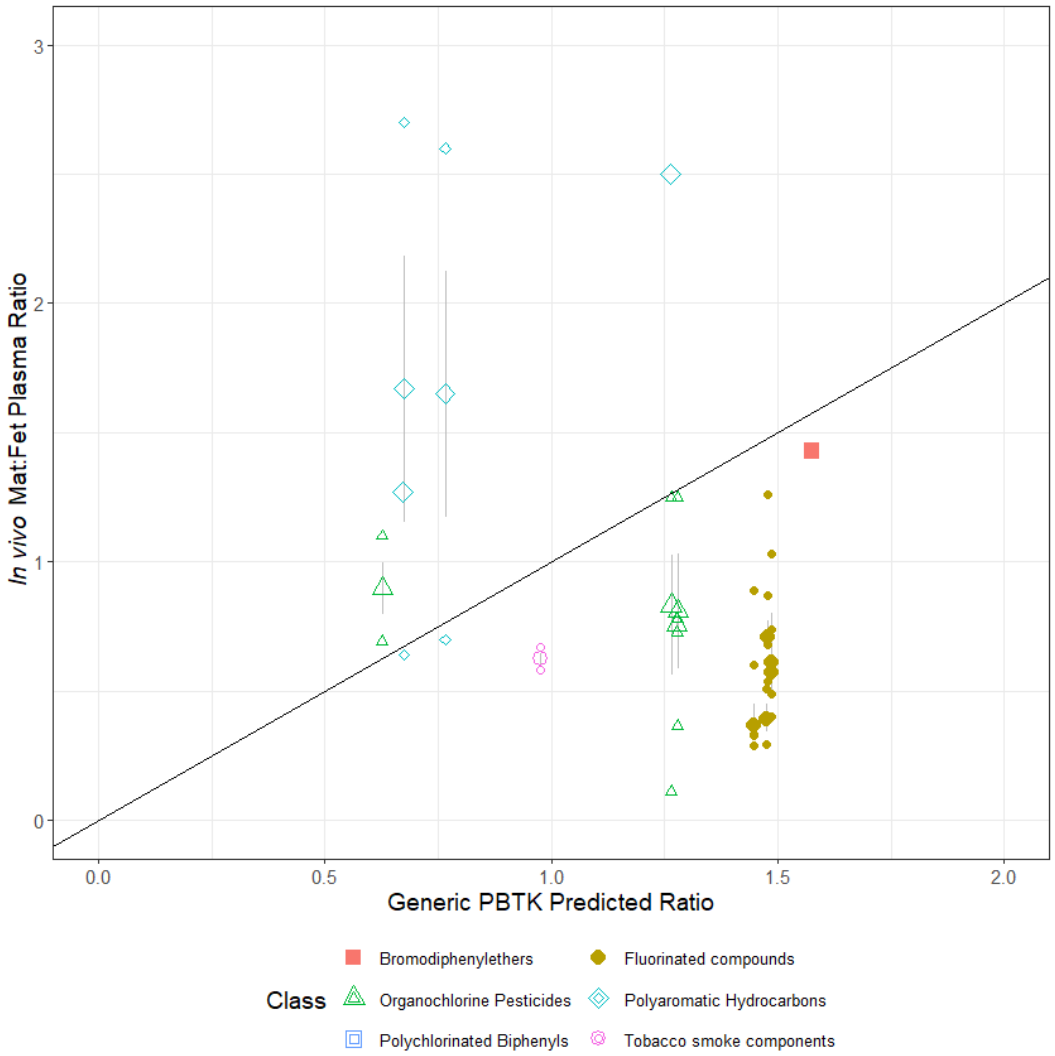
- Changes in maternal metabolic enzyme expression levels and activity
- Changes in fetal metabolic enzyme expression levels and activity
- Changes in renal clearance capacities in fetus across gestational age
- Changes in plasma protein binding for both mother and fetus
- Placental metabolism contributions
- Placental barrier descriptions (permeability rate constants or active transporter function to determine extent of fetal exposure might be important for some chemicals)
- Blood-brain barrier descriptions (permeability rate constants or active transporter function)

PBTK Model Evaluation Results

Model B

- Aylward et al. (2014) collated data for ratios of maternal and cord blood concentrations for 88 unique chemicals from over 100 studies.
  - HTTK were data available for 26 of the chemicals.
  - Omitting volatile chemicals, 9 remain.
- We compared observed ratios (Aylward et al., 2014) and model-predicted maternal-to-fetal plasma concentration ratios at term.
- For each chemical, there is a single prediction (x-value) but there are potentially multiple observations (y-values).
  - Larger symbol → median observation
  - Vertical line → interquartile range (IQR)
  - Smaller symbols → outliers

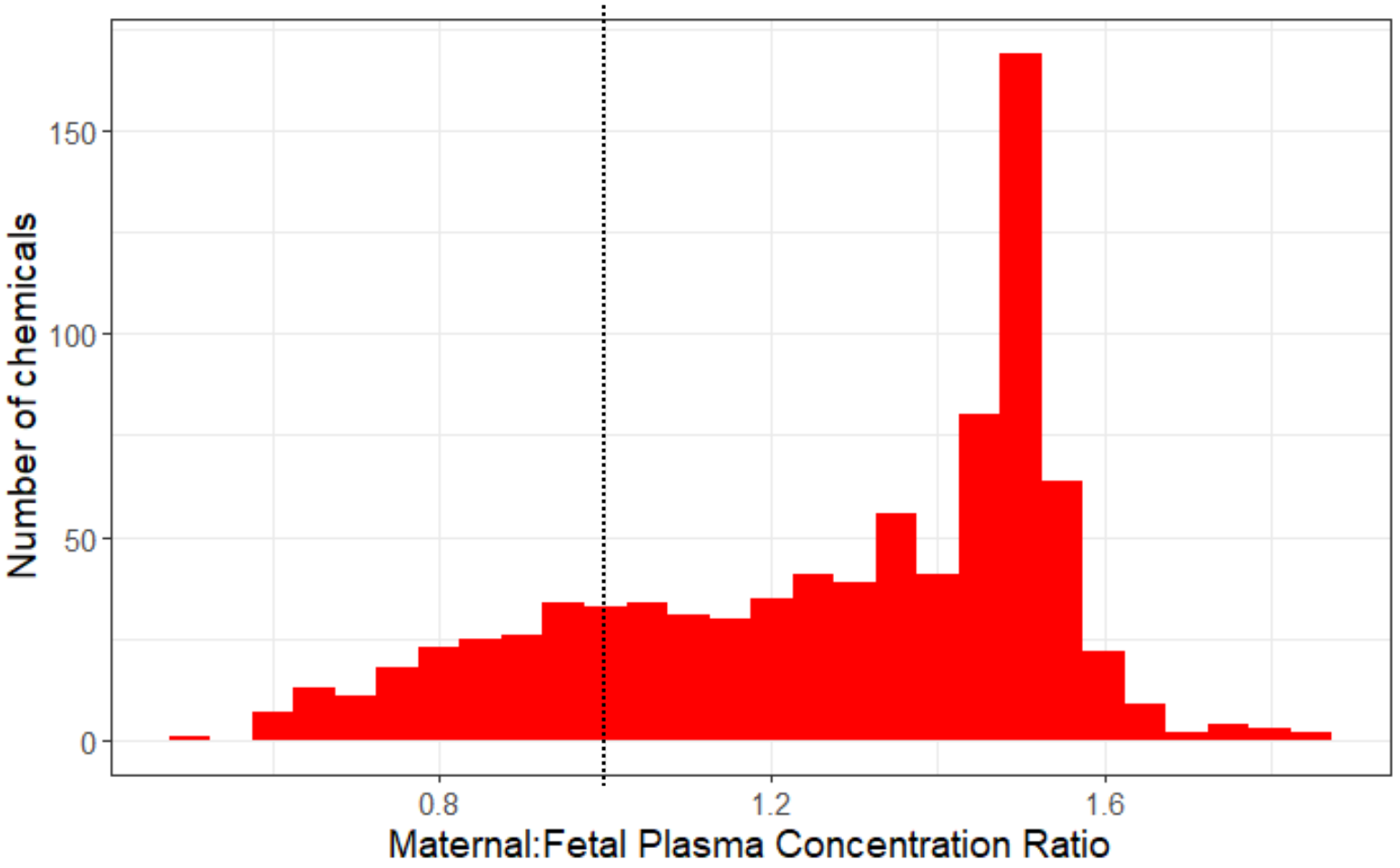
Maternal-to-Fetal Plasma Concentration Ratio



Maternal-to-Fetal Plasma Ratios

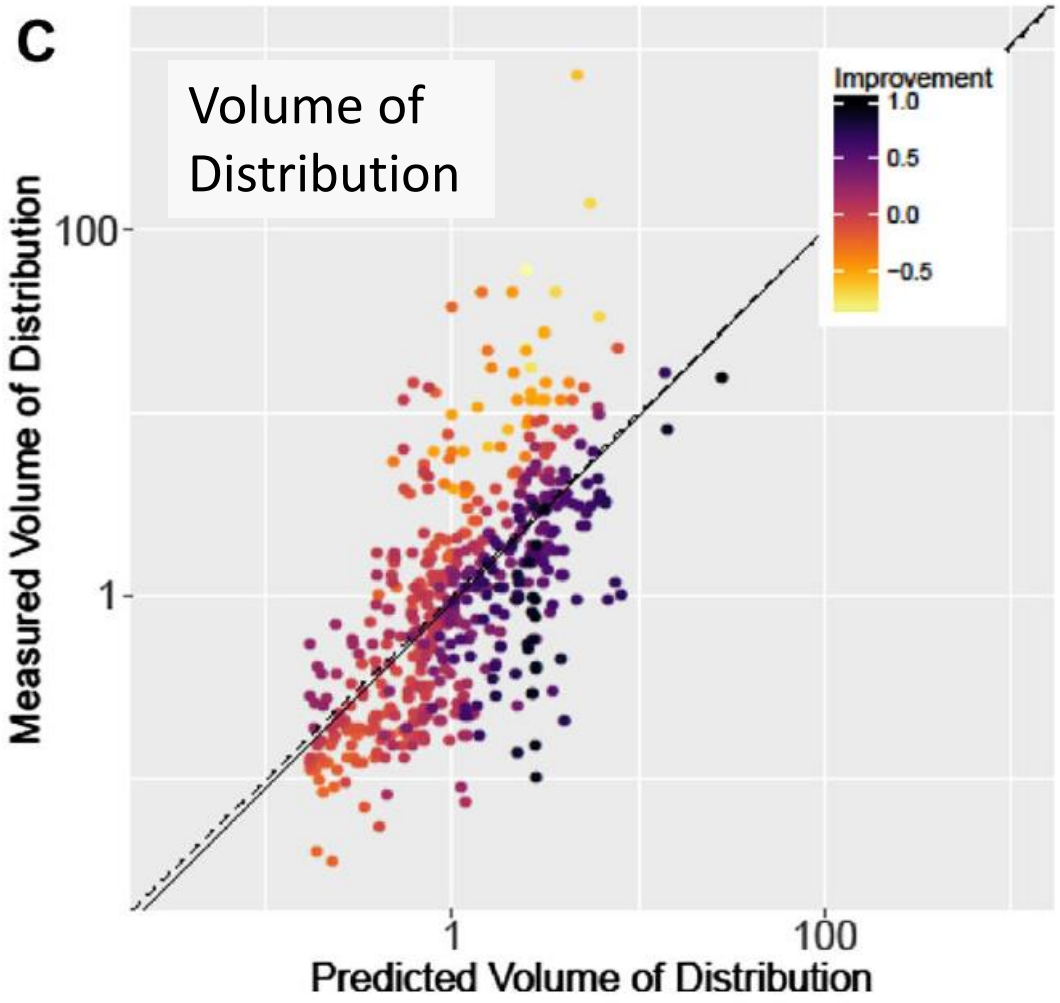
Model B

Histogram of predicted maternal-to-fetal plasma concentration ratios across the chemicals for which the HT-PBTK model can be parameterized (omitting volatile and semi-volatile chemicals).



HTTK Model Calibration and Evaluation

- HTTK attempts to trade precision for broad applicability
- Goal is to make reasonable predictions for many chemicals rather than accurate predictions for any specific chemical
- We can statistically characterize the error in the predictions

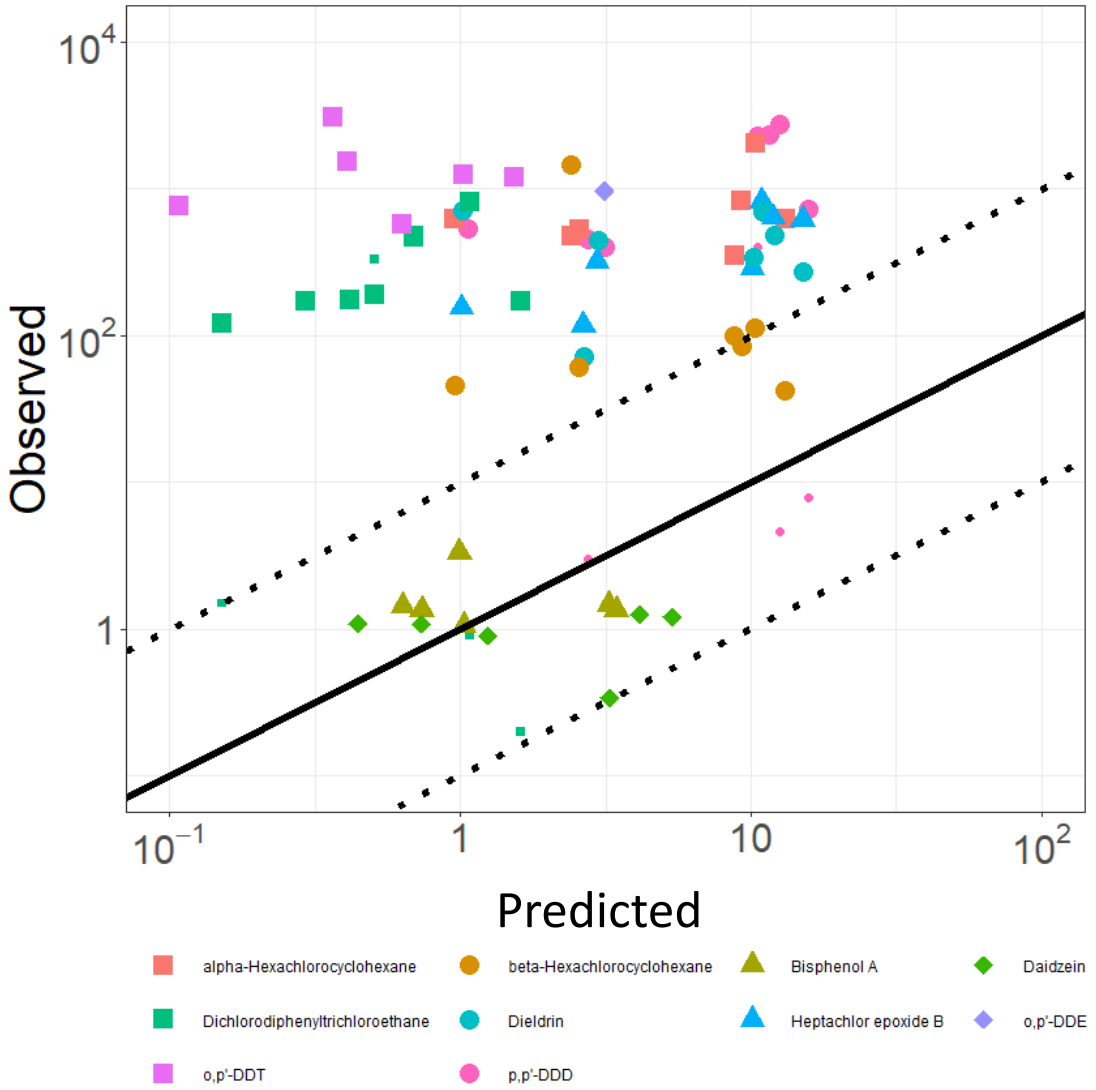


(Pearce et al., 2017b)

Fetal Partition Coefficients

Model B

- Fetal tissue-to-blood partition coefficients were determined by Curley et al. (1969) for six pesticides and seven tissues for which we can make predictions with the HT-PBTK model.
- Partition coefficients for tissues, including placenta, were measured *in vitro* by Csanády et al. (2002) for bisphenol A and daidzein.
- Small plot points indicate model-predicted, rather than measured, partition coefficients from Weijs et al. (2013) for three of the Curley et al. (1969) chemicals.
- The identity line (solid) indicates a perfect (1:1) prediction while the dotted lines indicate a ten-fold error.



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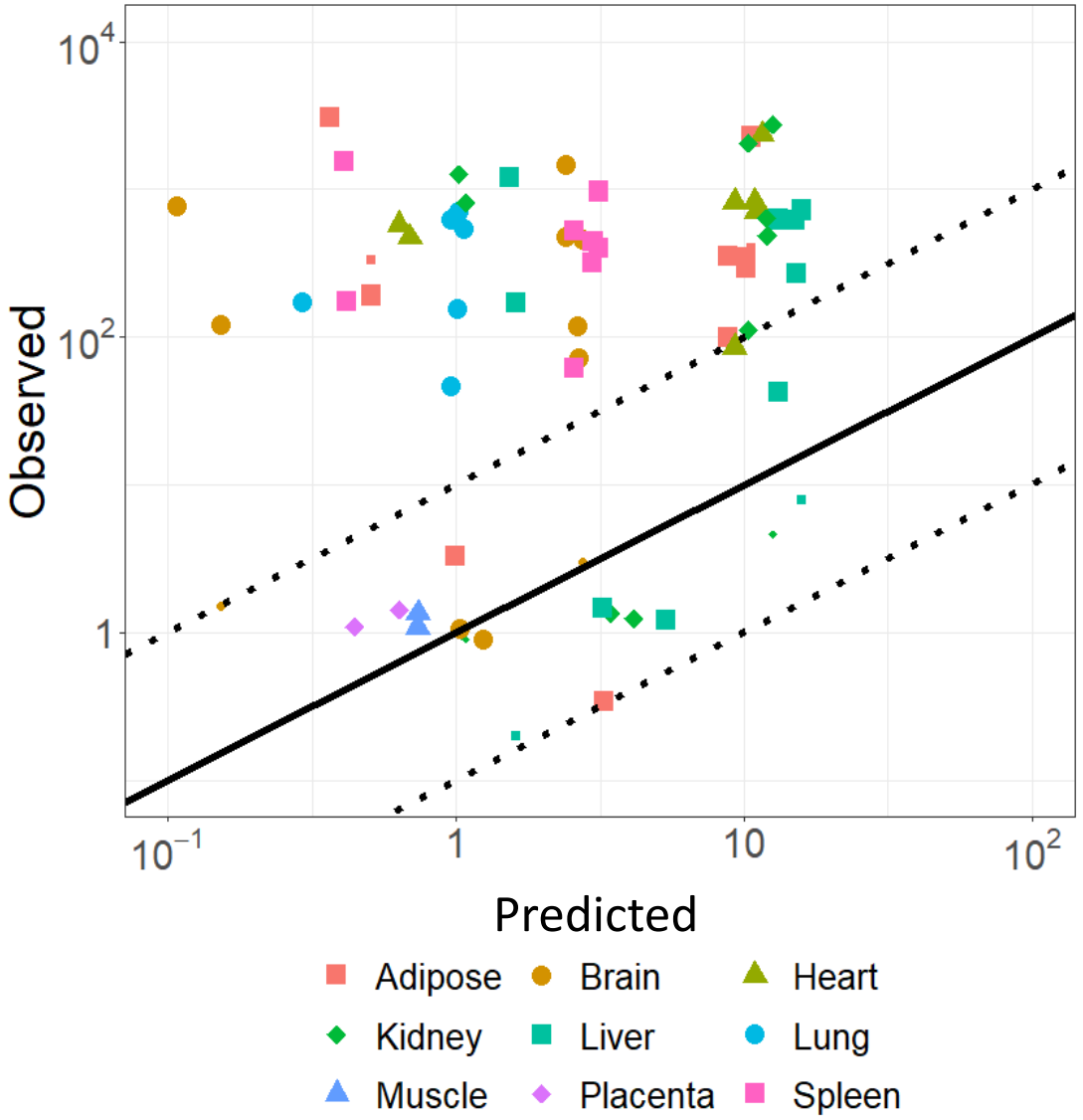
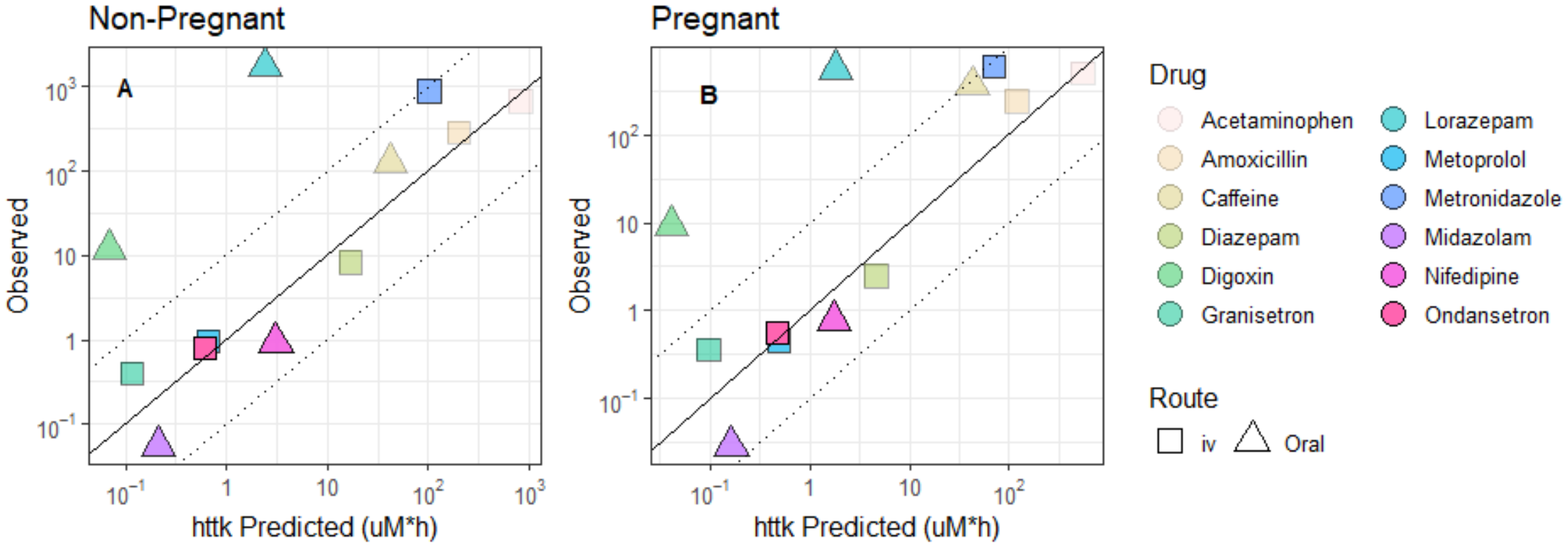


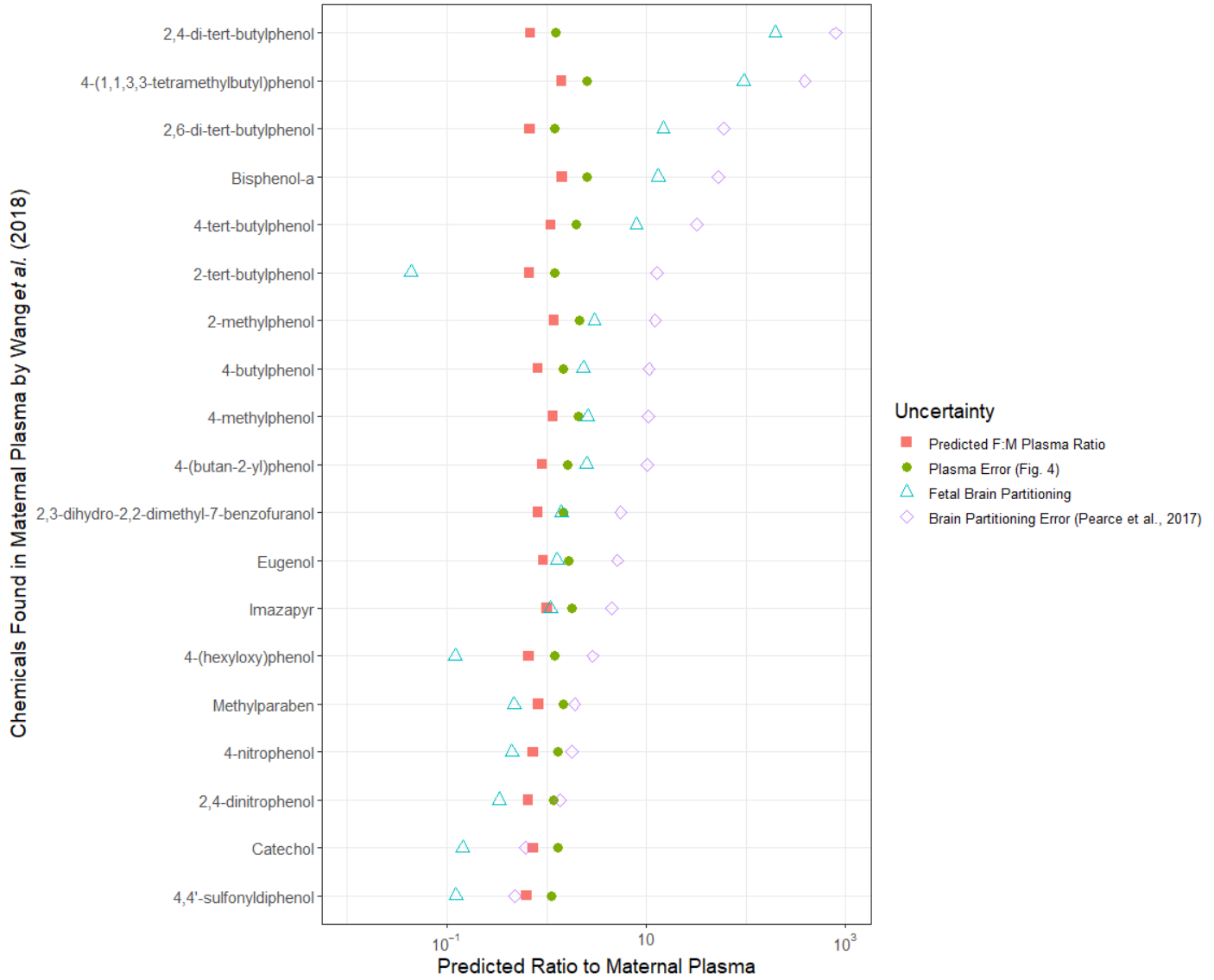
Observed AUCs

Comparison of observed (Dallmann et al., 2018) and predicted time-integrated plasma concentrations (AUCs) for twelve pharmaceuticals administered to non-pregnant (left) and pregnant (right) women.



Prioritizing Chemicals Detected in Maternal Plasma

- Wang et al. (2018) detected xenobiotic chemicals in the plasma of expectant mothers – here we prioritize those chemicals with respect to potential concentration in the fetal brain
- Ordered from the top are those chemicals with the highest predicted fetal brain concentrations relative to maternal blood
- Estimated error (uncertainty) propagated using upper 95th percentiles



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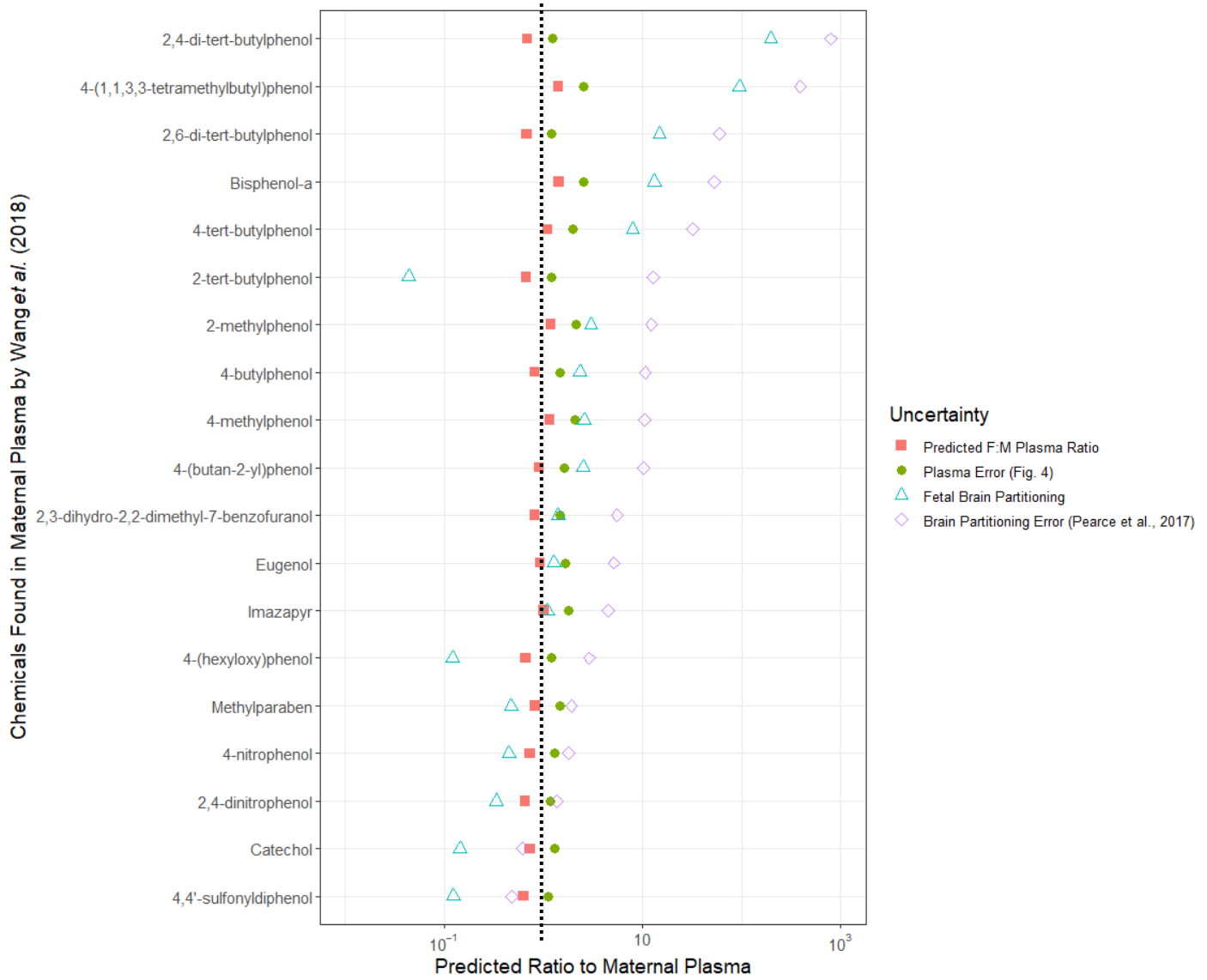

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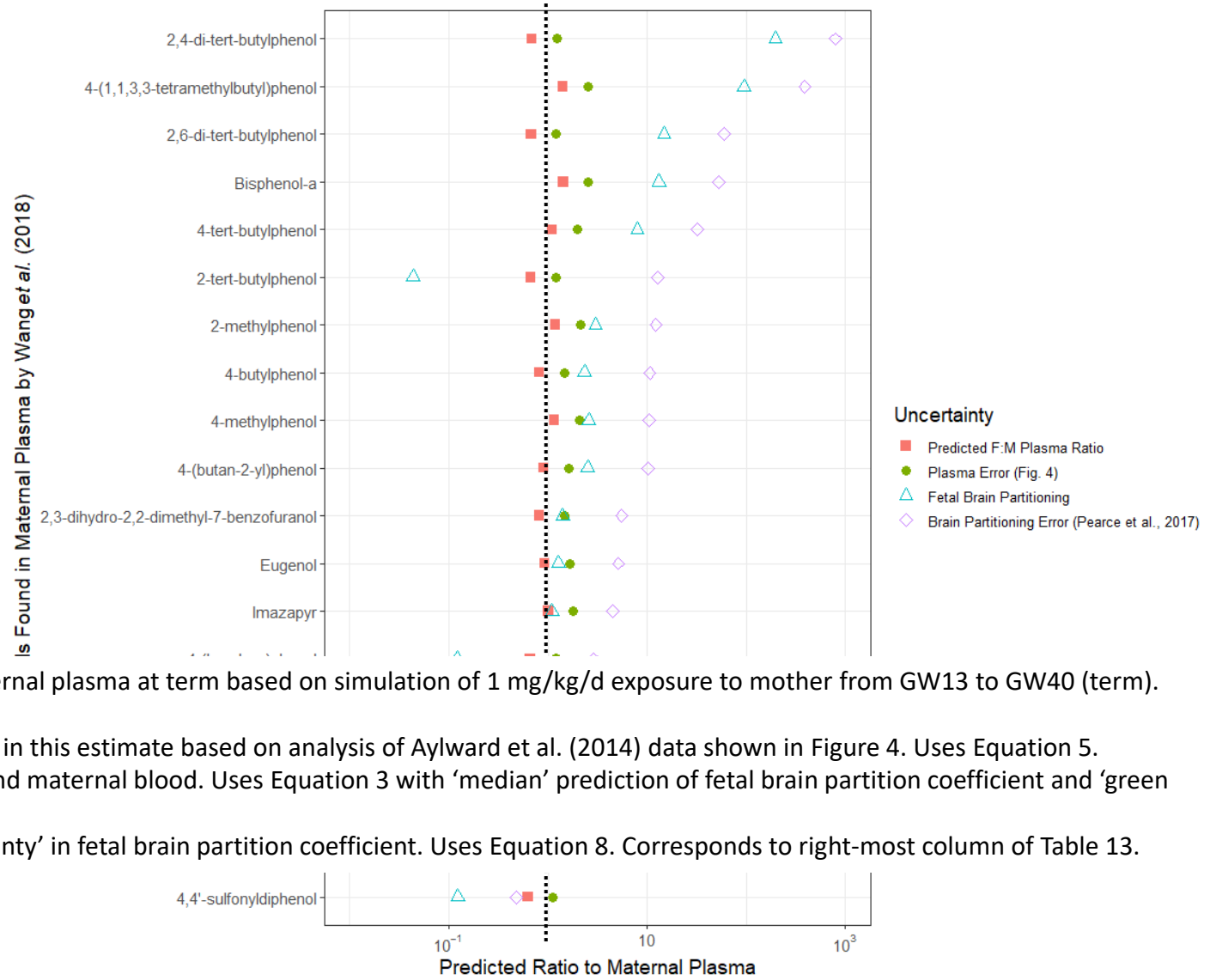
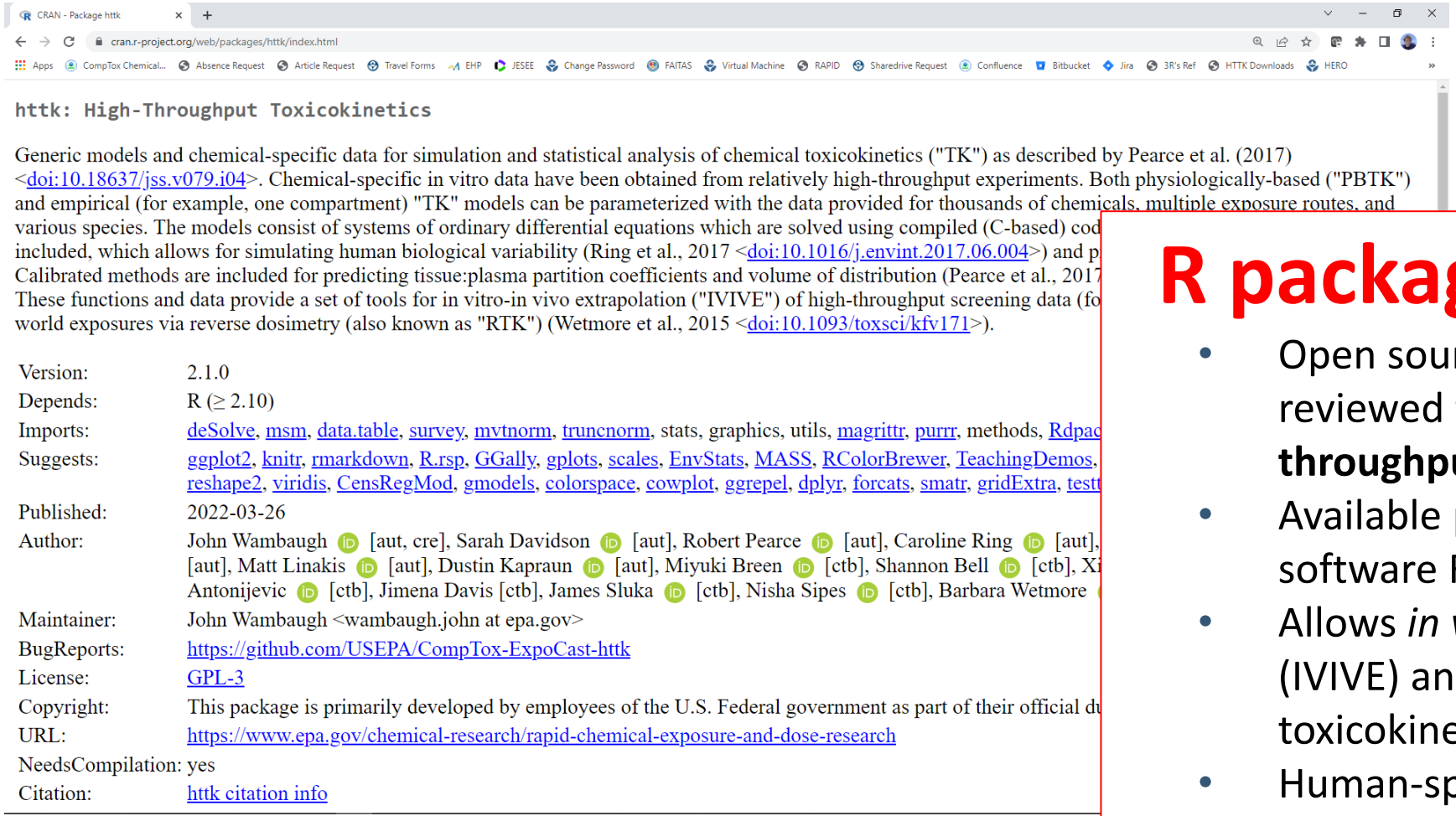


- **Red Square:** Estimate of ratio of concentrations in fetal and maternal plasma at term based on simulation of 1 mg/kg/d exposure to mother from GW13 to GW40 (term). Corresponds to $R_{\mathrm{fet:mat}}$ column of Table 13.
- **Green Circle:** Estimate of same after accounting for 'uncertainty' in this estimate based on analysis of Aylward et al. (2014) data shown in Figure 4. Uses Equation 5.
- **Blue Triangle:** Estimate of ratio of concentrations in fetal brain and maternal blood. Uses Equation 3 with 'median' prediction of fetal brain partition coefficient and 'green circle' value of f:m plasma ratio.
- **Purple Diamond:** Estimate of same after accounting for 'uncertainty' in fetal brain partition coefficient. Uses Equation 8. Corresponds to right-most column of Table 13.

"Model B" Included in httk Version 2.1.0

https://CRAN.R-project.org/package=httk



CRAN - Package httk

cran.r-project.org/web/packages/httk/index.html

httk: High-Throughput Toxicokinetics

Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics ("TK") as described by Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from relatively high-throughput experiments. Both physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" models can be parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species. The models consist of systems of ordinary differential equations which are solved using compiled (C-based) cod included, which allows for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and p Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high-throughput screening data (fo world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Version:	2.1.0
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, purrr, methods, Rdpac
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, reshape2, viridis, CensRegMod, gmodels, colorspace, cowplot, ggrepel, dplyr, forcats, smatr, gridExtra, testt
Published:	2022-03-26
Author:	John Wambaugh [aut, cre], Sarah Davidson [aut], Robert Pearce [aut], Caroline Ring [aut], [aut], Matt Linakis [aut], Dustin Kapraun [aut], Miyuki Breen [ctb], Shannon Bell [ctb], Xi Antonijevic [ctb], Jimena Davis [ctb], James Sluka [ctb], Nisha Sipes [ctb], Barbara Wetmore
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
BugReports:	https://github.com/USEPA/CompTox-ExpoCast-httk
License:	GPL-3
Copyright:	This package is primarily developed by employees of the U.S. Federal government as part of their official du
URL:	https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research
NeedsCompilation:	yes
Citation:	httk citation info

R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Described in Pearce et al. (2017)

Summary (Model B)

- We developed a generic **PBTK model** that can be used to simulate ADME in a **human mother and fetus** during **pregnancy** and **gestation**.
  - Model is compatible with pre-existing in vitro data for nearly 1000 chemicals.
- We **evaluated** our **PBTK model** using available data, including:
  - Paired observations of cord and maternal blood concentrations
  - Observations of concentrations in pregnant women
- We **demonstrated** how the PBTK model can be used to estimate fetal brain concentrations based on maternal blood concentrations.
- Our PBTK model can be used to estimate concentrations in fetal tissues (e.g., brain) based on concentration in maternal blood, along with uncertainty, and thus could potentially be used for prioritization of chemicals (e.g., chemicals with developmental toxicity potential).

Comparing Model Features

Feature	Model A	Model B
Generic (can be parameterized for many chemicals)	●	●
Focused on LPECs	●	
Classical PK model	●	
PBTK model		●
Includes time-varying parameters	●	●
Covers pregnancy and gestation	●	●
Covers lactation	●	
Parameterized for humans	●	●
Parameterized for laboratory animals	●	

United States Environmental Protection Agency

Thank you!

Dustin Kapraun

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