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United States Environmental Protection Agency

Evaluation of a Rapid, Generic Human Gestational Dose Model

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Office of Research and Development
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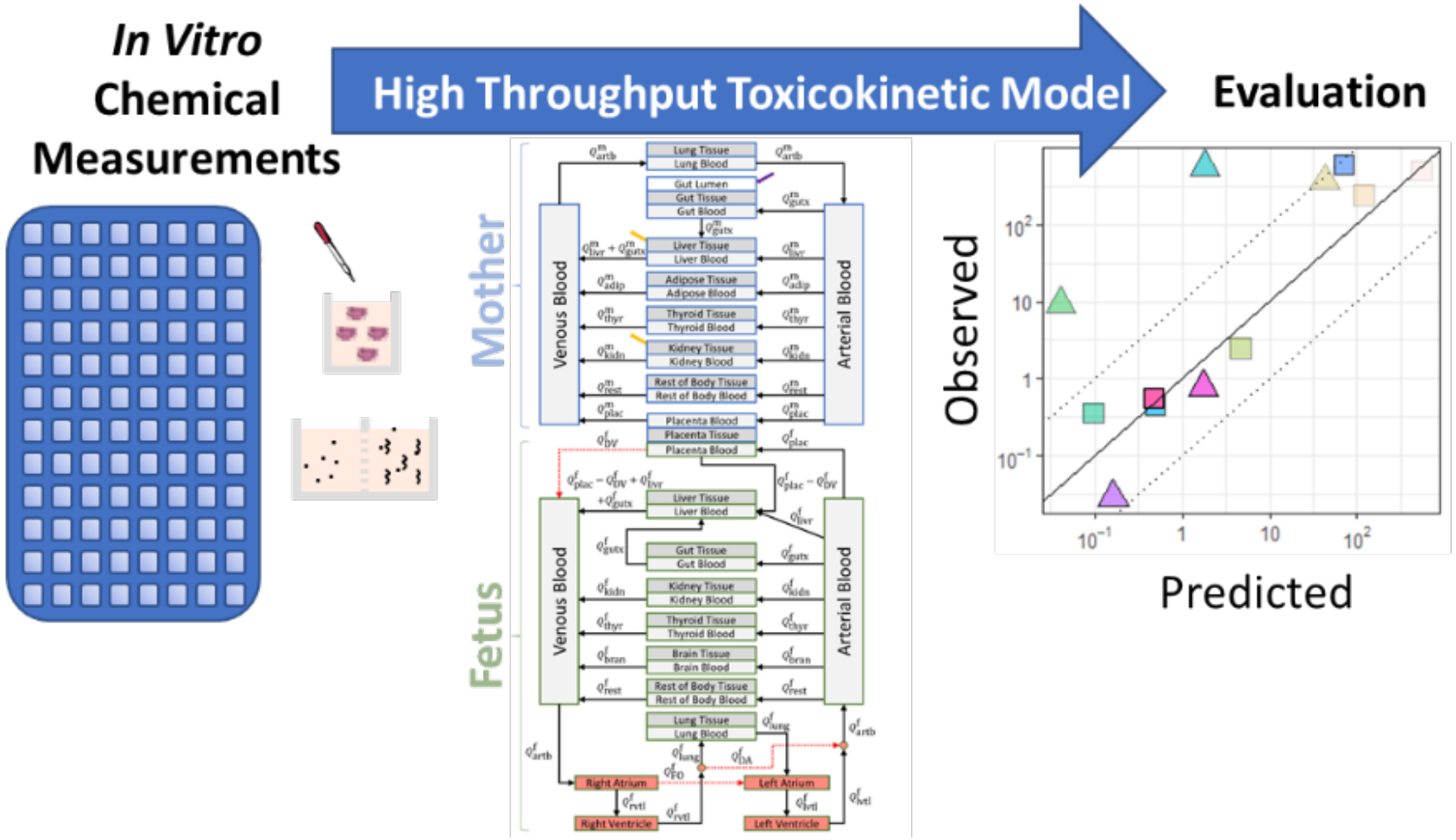
Graphical Abstract



‘HTTK’ R-Package Extended to Pregnancy

1-Comp 3-Comp PBTK Maternal/Fetal PBTK

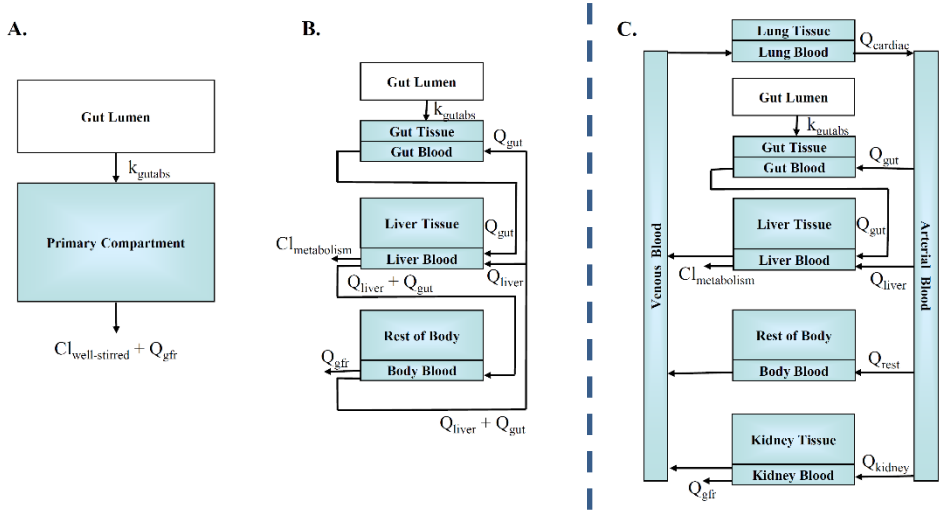


Figure 1: Models (A) 1compartment, (B) 3compartment, and (C) pbtk. In order to preserve mass-balance, Q_{rest} is defined as the difference between $Q_{cardiac}$ and the flow to the liver, kidney, and gut. Variable names are defined in Table 1.

Pearce et al. 2017a

PLOS ONE

RESEARCH ARTICLE

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

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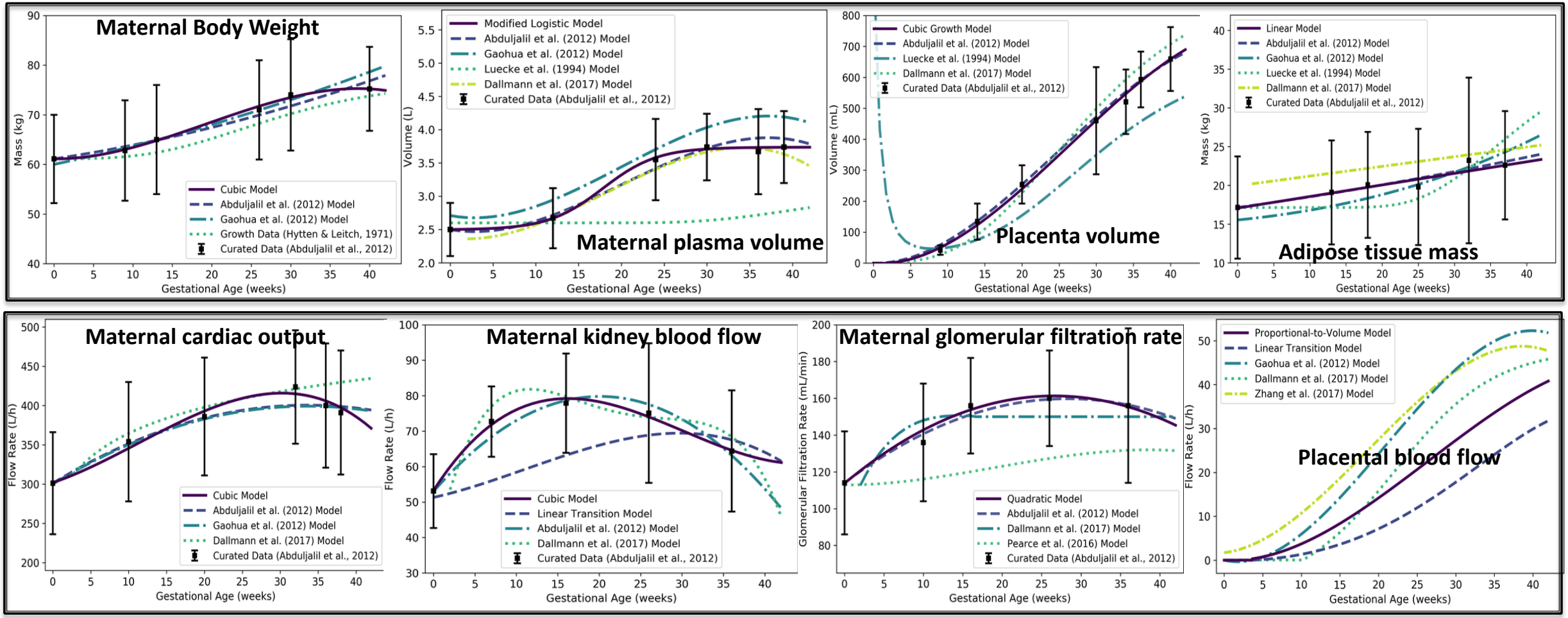
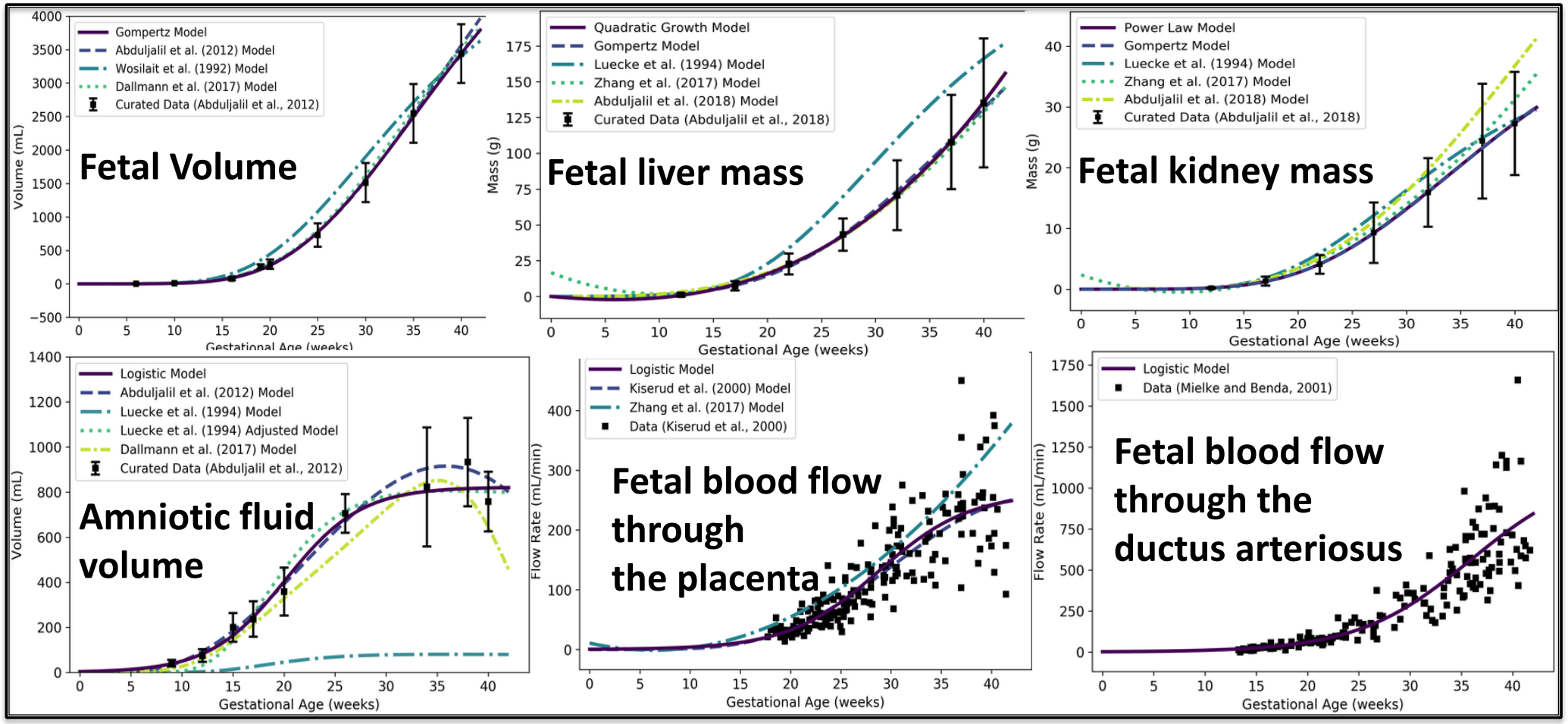
Kapraun et al. 2019

Representative Physiological Parameter Changes in the Mother



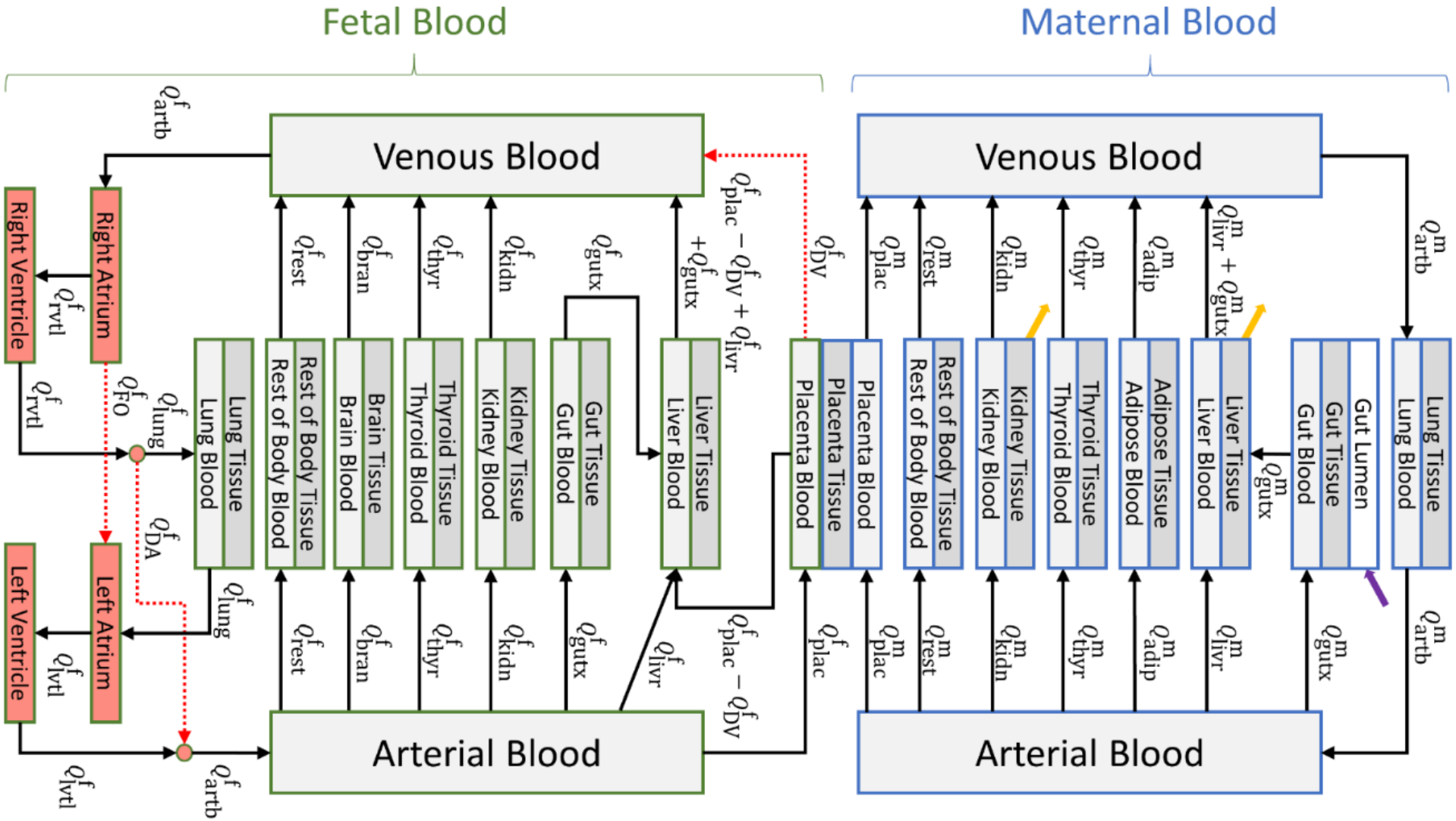
Kapraun et al. (2019)

Representative Physiological Parameter Changes in the Fetus



Kapraun et al. (2019)

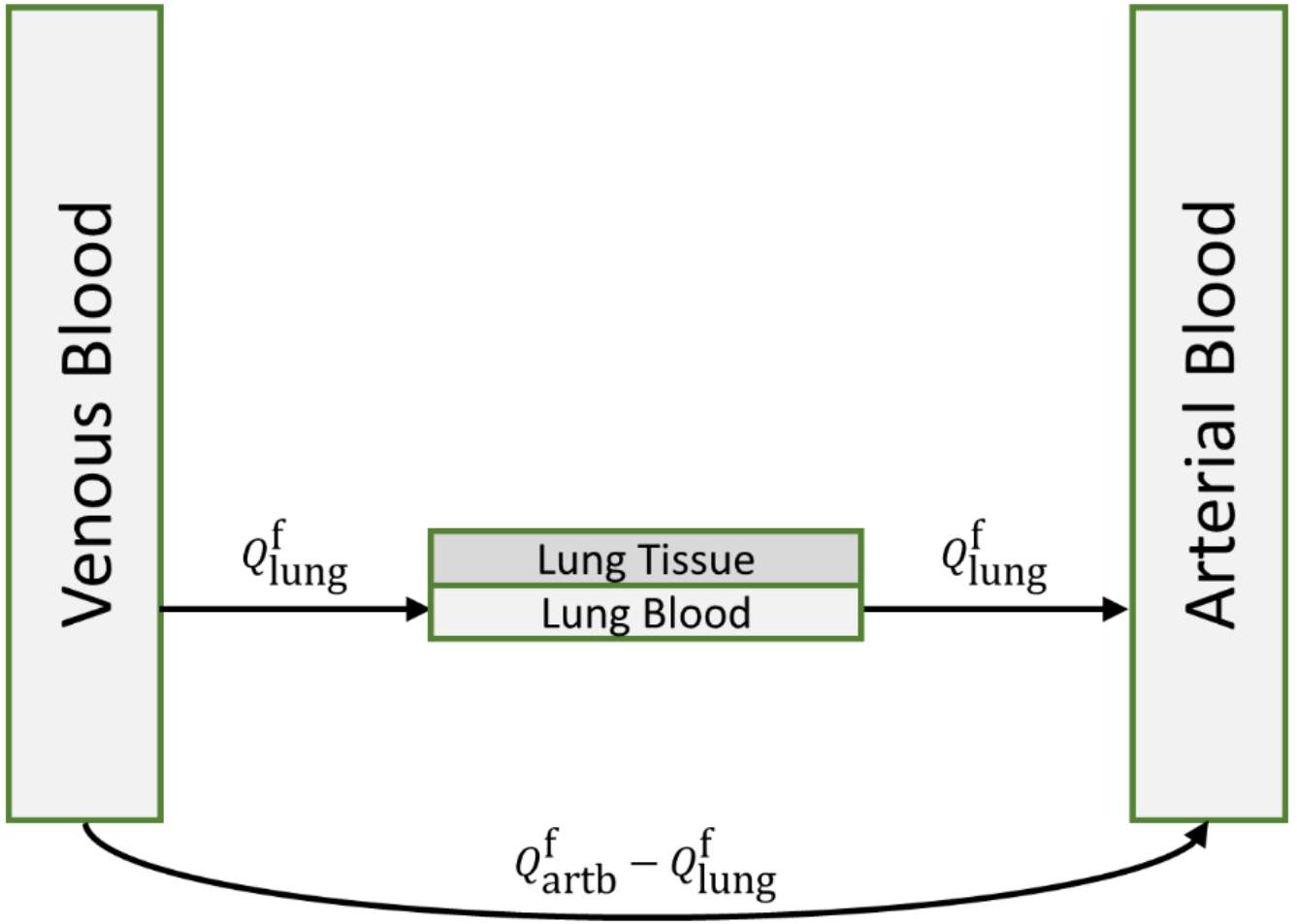
Generic Gestational PBTK Model



Kapraun et al. (submitted)

Fetal Heart

- Simplified partial schematic diagram illustrating effective blood flows in the vicinity of the fetal heart.

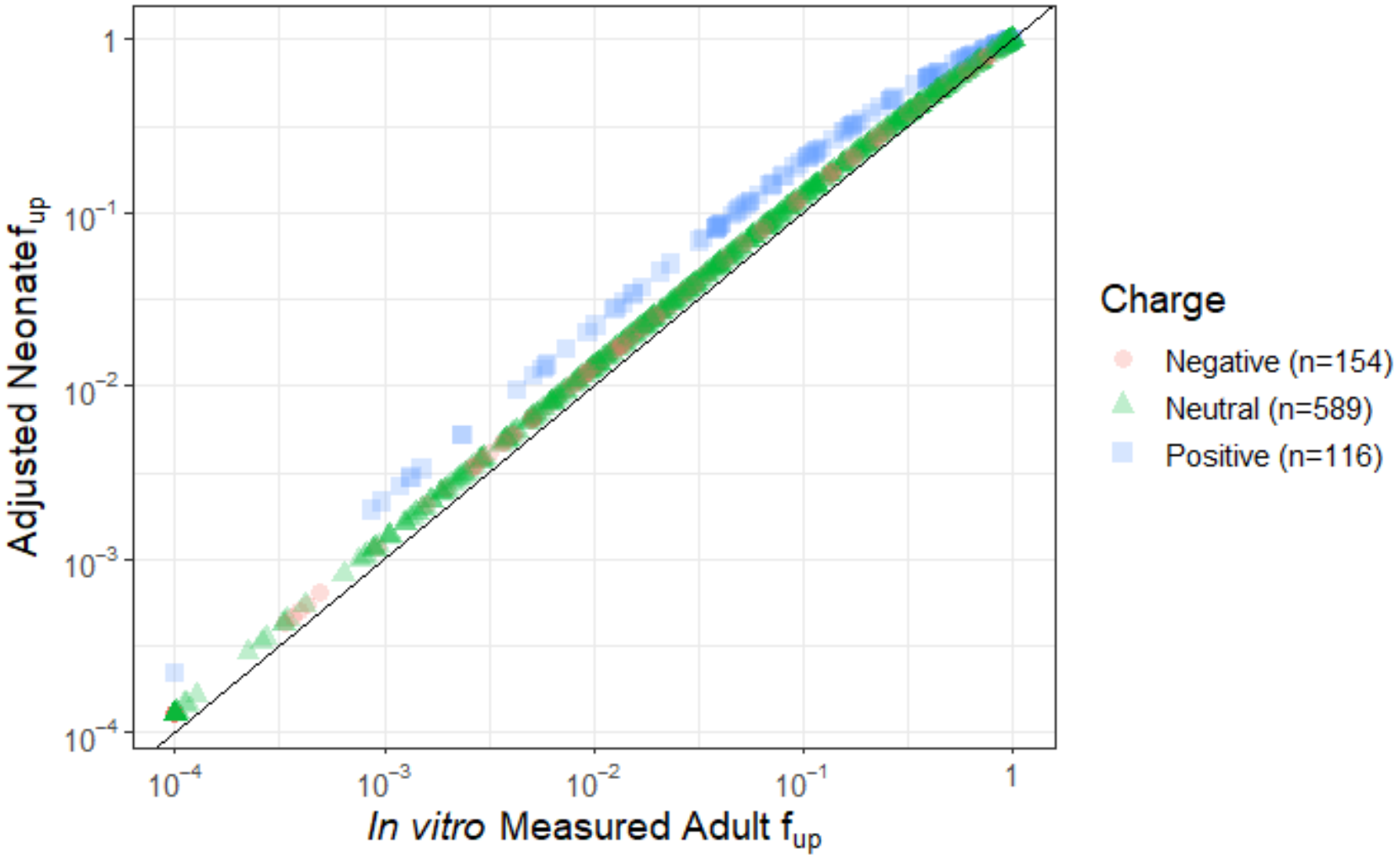


Kapraun et al. (submitted)

Adjusting Plasma Binding

- The fetal fraction unbound (f_{up}^{f}) is calculated from the maternal fraction unbound and the serum protein concentration ratio in infants vs. mothers based on Equation 6 of [McNamara and Meiman (2019)]:

$$f_{up}^{f} = \frac{f_{up}^{m}}{f_{up}^{m} + (P^{f}/P^{m}) \times \left(1 - f_{up}^{m}\right)},$$



Kapraun et al. (submitted)

Maternal/Fetal HTTK Model: Features

- 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 weight, blood flow rate, and compartment volumes) 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 >900 chemicals

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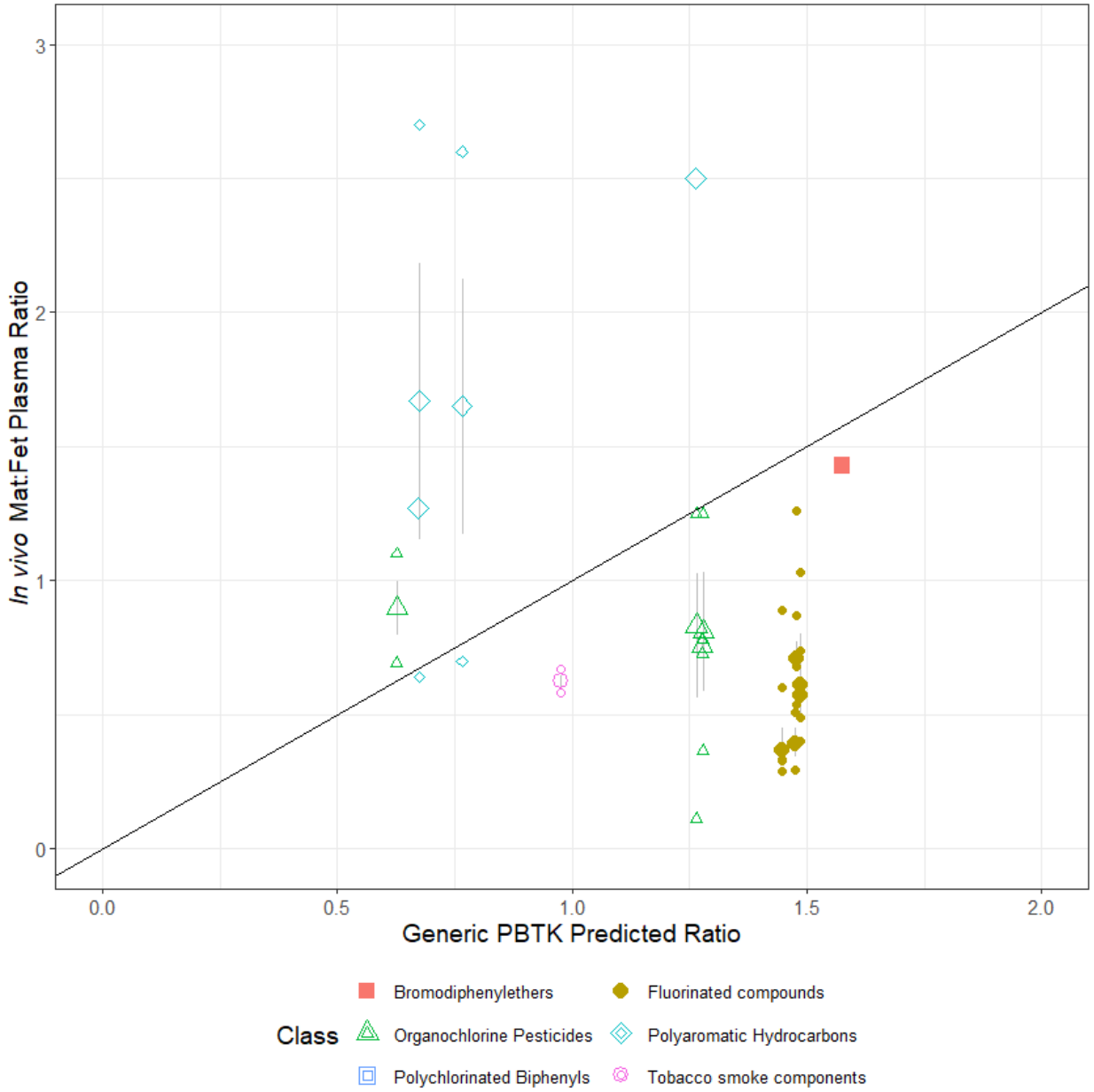
Maternal/Fetal HTTK Model: Not Included

- 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 mom 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)

Kapraun et al. (submitted)

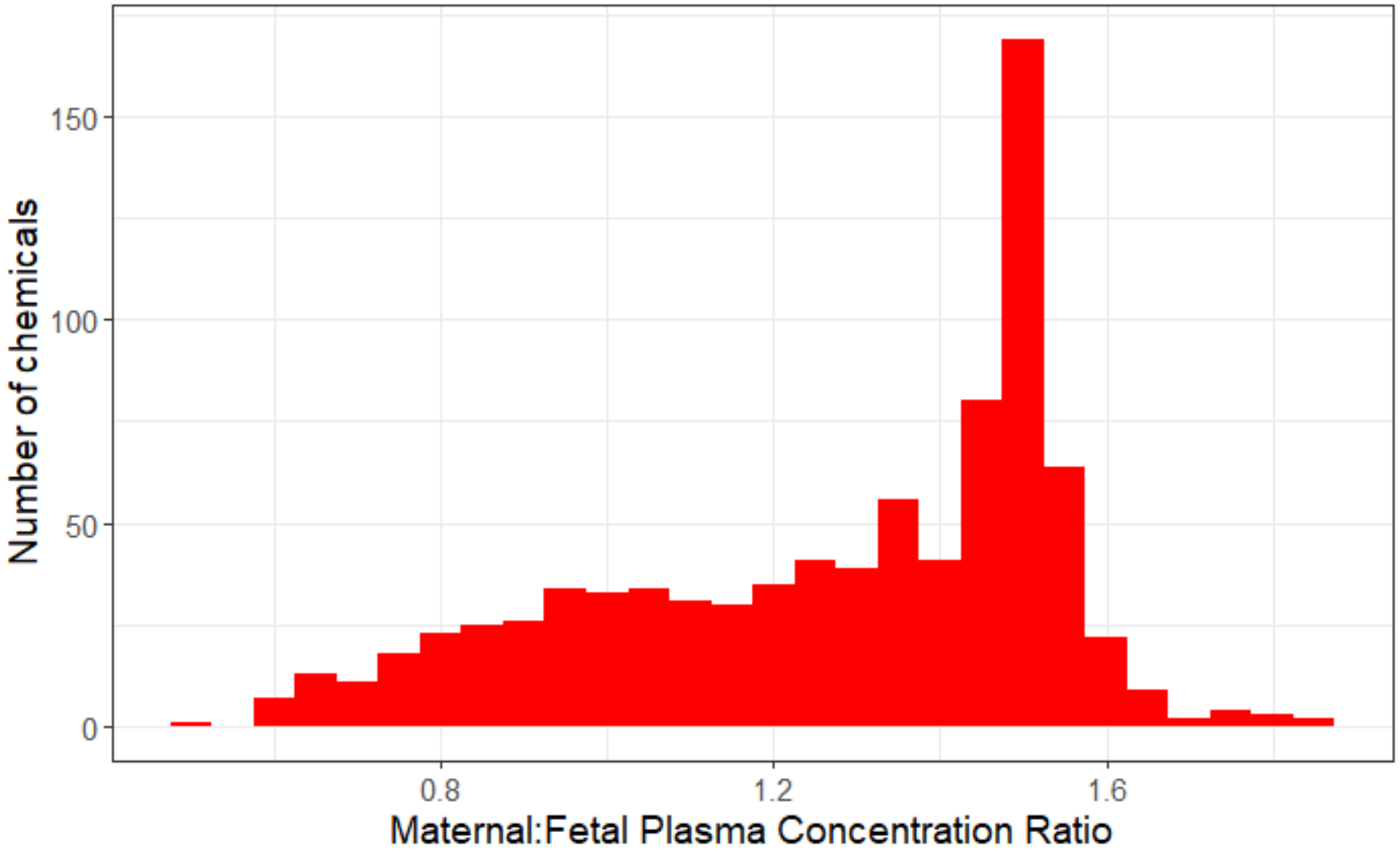
Observed Maternal:Fetal Plasma Ratio

- Comparison between observed (Aylward et al., 2014) and predicted maternal-to-fetal plasma concentration ratios at birth. The identity line (solid) indicates a perfect (1:1) correspondence between predictions and observations.
- For any one chemical there is a single prediction (x-value) but there are potentially multiple observations (y-values). The median observation is plotted with a larger symbol, while the 75% interval is depicted with a vertical line and outliers beyond that range are plotted with smaller symbols.



Predicted Maternal:Fetal Plasma Ratio

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



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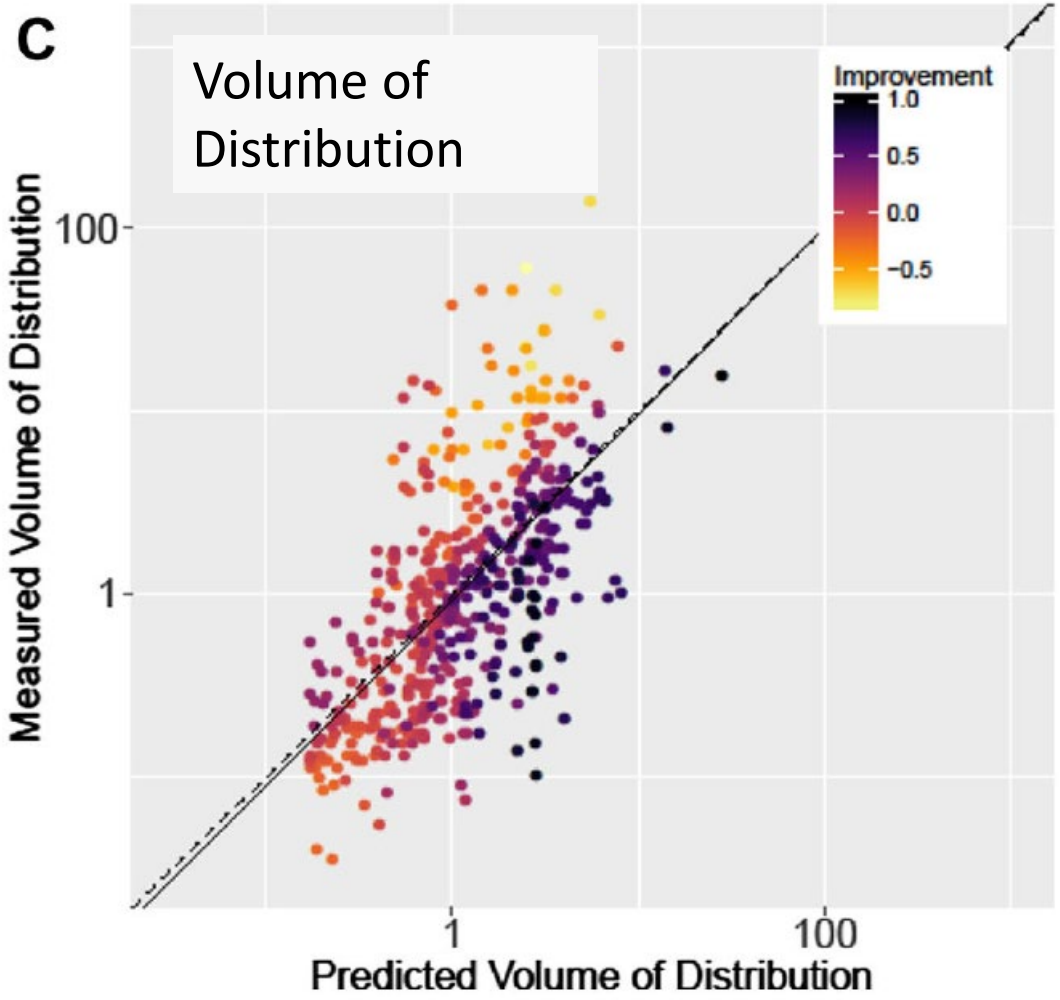
HTTK Model Calibration and Evaluation

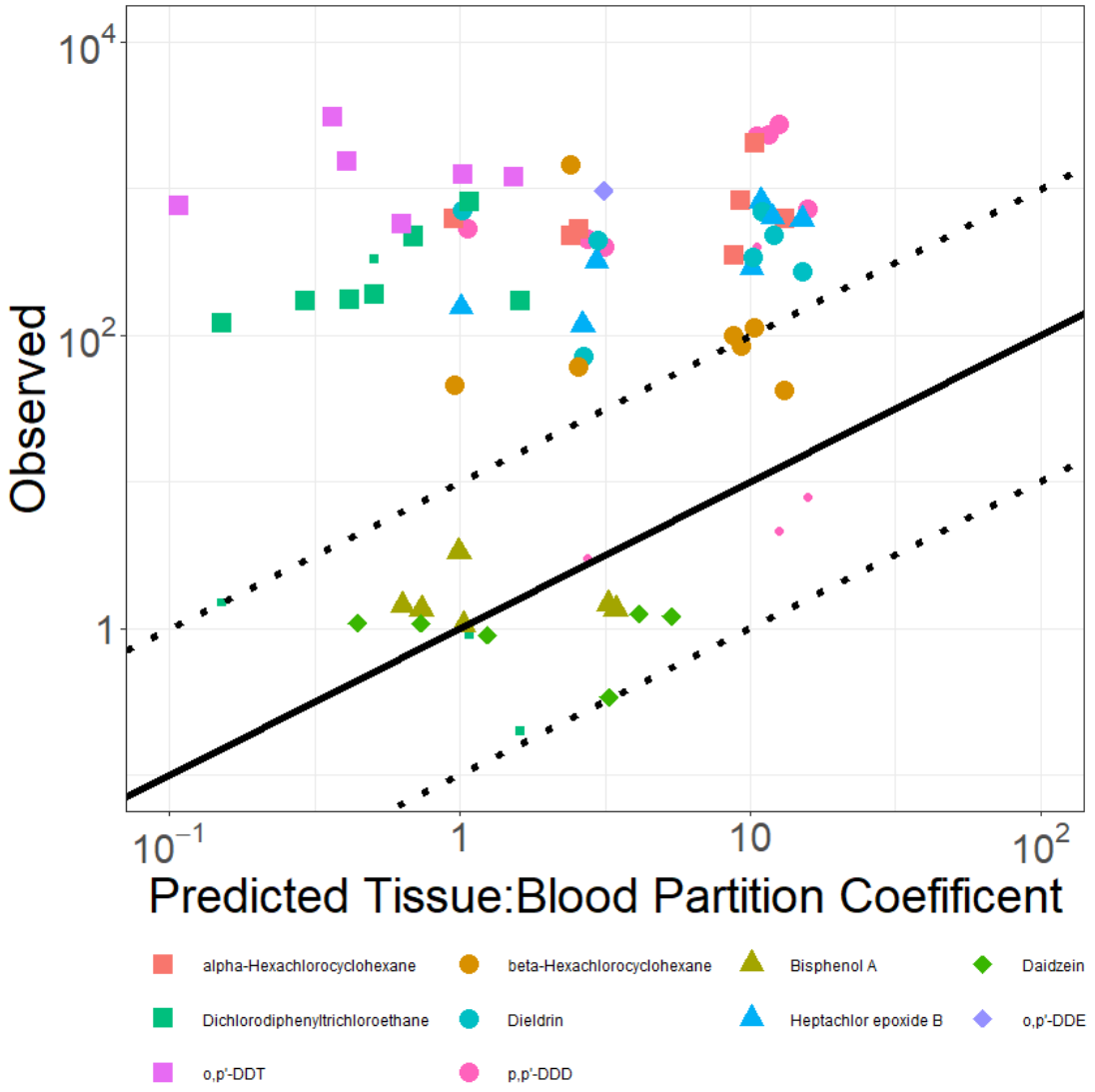
- HTTK attempts to trade precision for broad applicability
- Goal is to make reasonable predictions for many chemicals rather than accurate predictions for a specific chemical
- We can statistically characterize the error in the predictions
- Data from Obach et al. (2008)



Pearce et al. 2017b

Observed Tissue Partition Coefficients

- 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 were measured for tissues, including placenta, *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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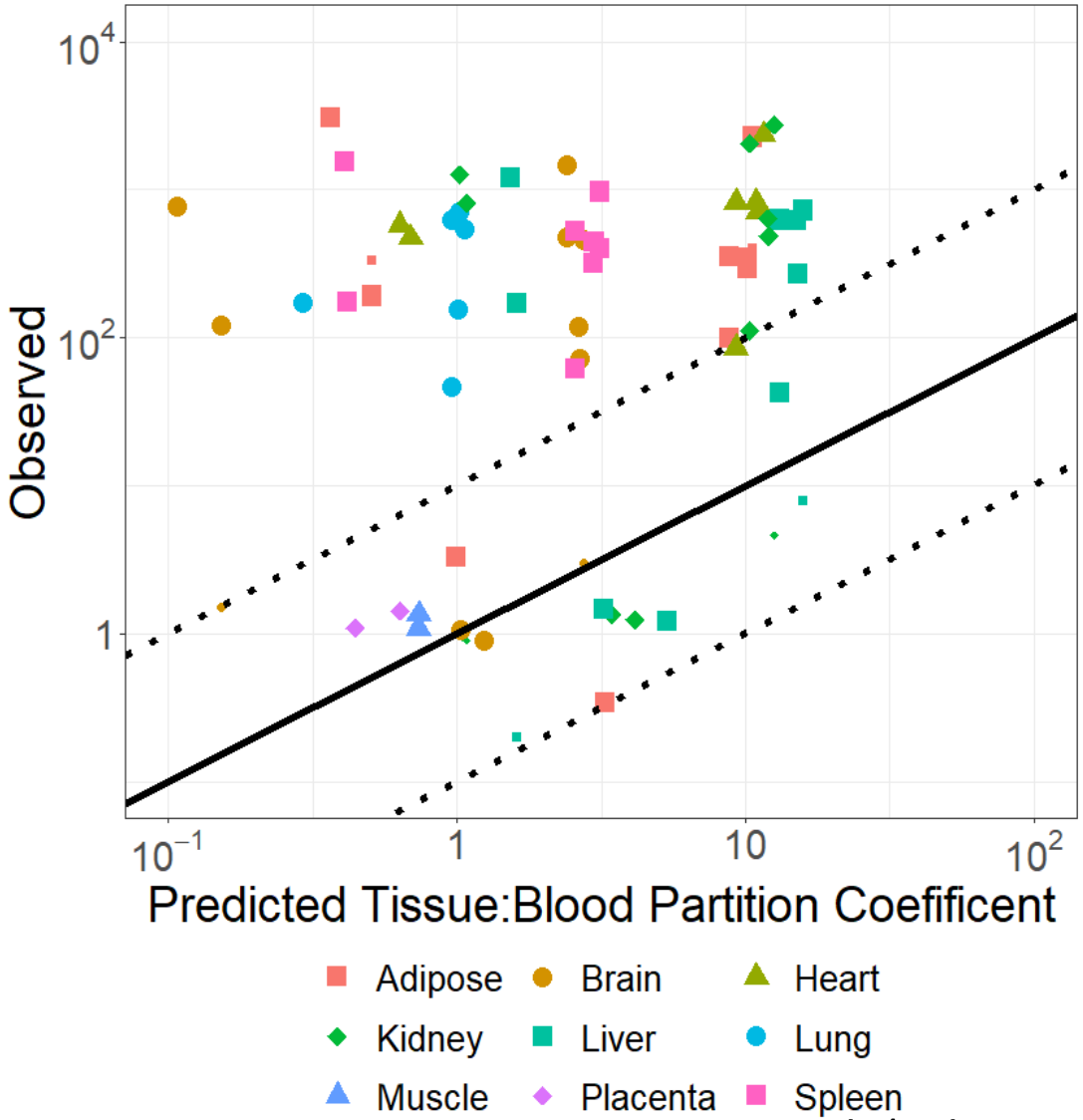
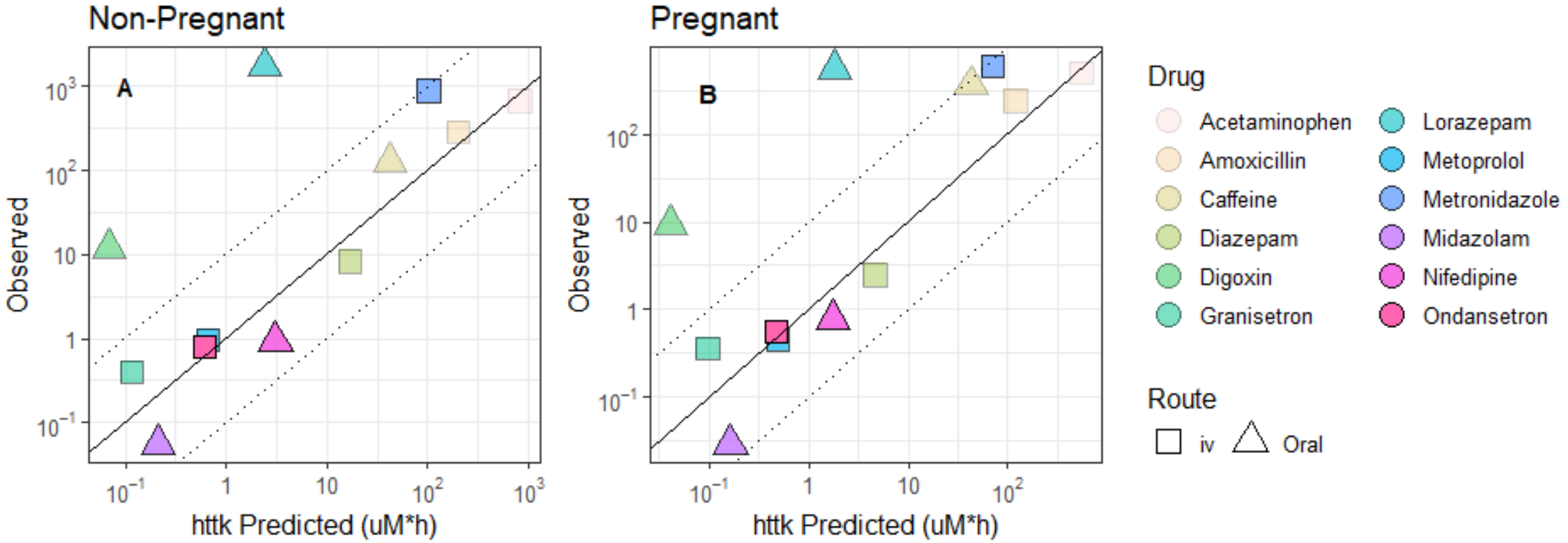


Kapraun et al. (submitted)

Observed Time Integrated Plasma Concentrations (AUC)

- Comparison of observed and predicted time-integrated plasma concentration (AUC) for the data in for non-pregnant (left) and pregnant (right) mothers across twelve pharmaceuticals (Data from Dallman et al., 2018).

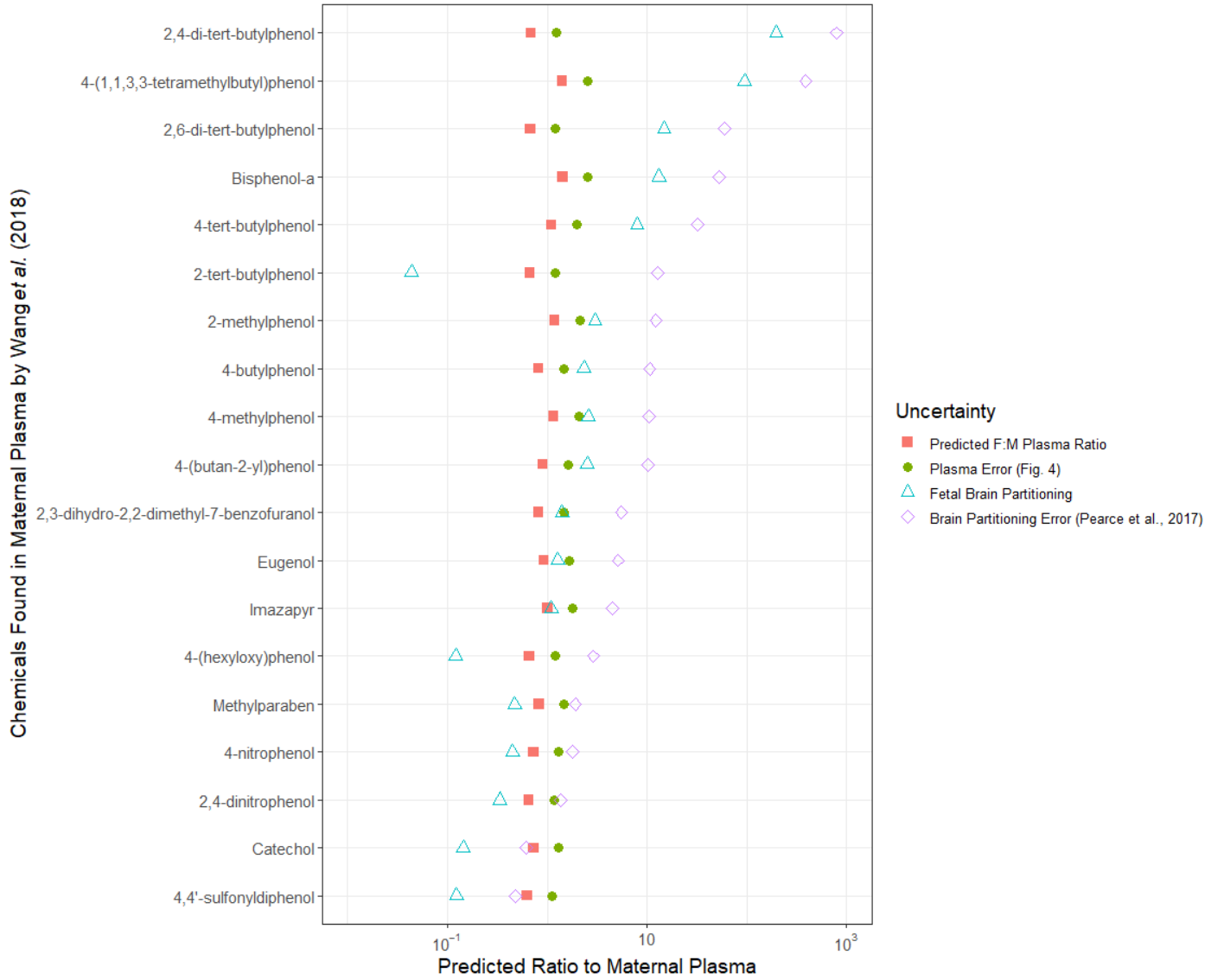


Kapraun et al. (submitted)

Kapraun et al. (submitted)

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



Gestational Model Included in v2.1.0

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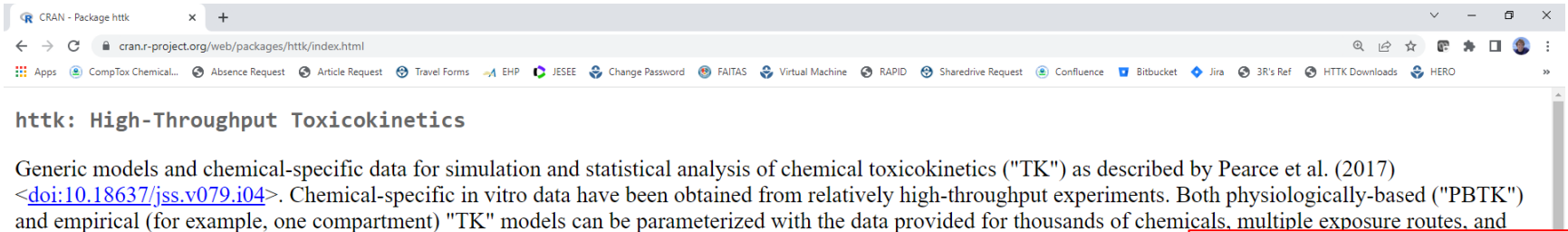
CRAN - Package httk

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

Apps CompTox Chemical... Absence Request Article Request Travel Forms EHP JESEE Change Password FAITAS Virtual Machine RAPID Sharedrive Request Confluence Bitbucket Jira 3R's Ref HTTK Downloads HERO

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)

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