Examining Models for the Pharmacokinetics of Perfluorooctanoic acid

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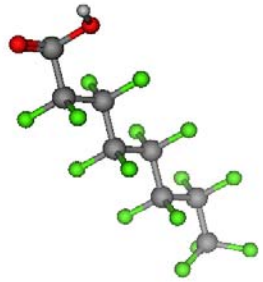
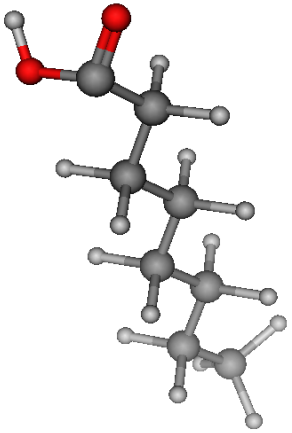
Perfluoroalkyll acids (PFAA)



Straight chain PFOA

- Perfluorooctanoic acid (PFOA) is a perfluorinated fatty acid analog (Other PFAAs include PFOS and PFNA)
- Found throughout the environment (Lau et al., 2007)
- Measurable levels in the blood serum of most people in the United States (Calafat et al., 2007)

- Production of PFOS was halted in 2002 in the United States (Betts, 2007) – some evidence that human serum levels decreasing (Olsen et al., 2007)
- Industry will work toward eliminating emissions and product content of PFOA and related chemicals by 2015
- Replacement chemicals are typically shorter length carbon chain compounds
- PFOA is not metabolized, making PK modeling somewhat “easier”



Caprylic acid

Pharmacokinetics of PFAA

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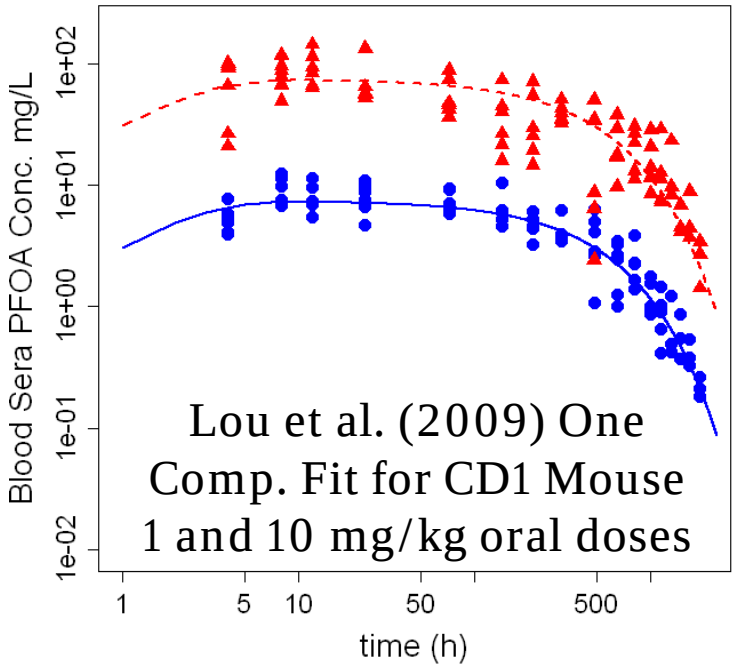
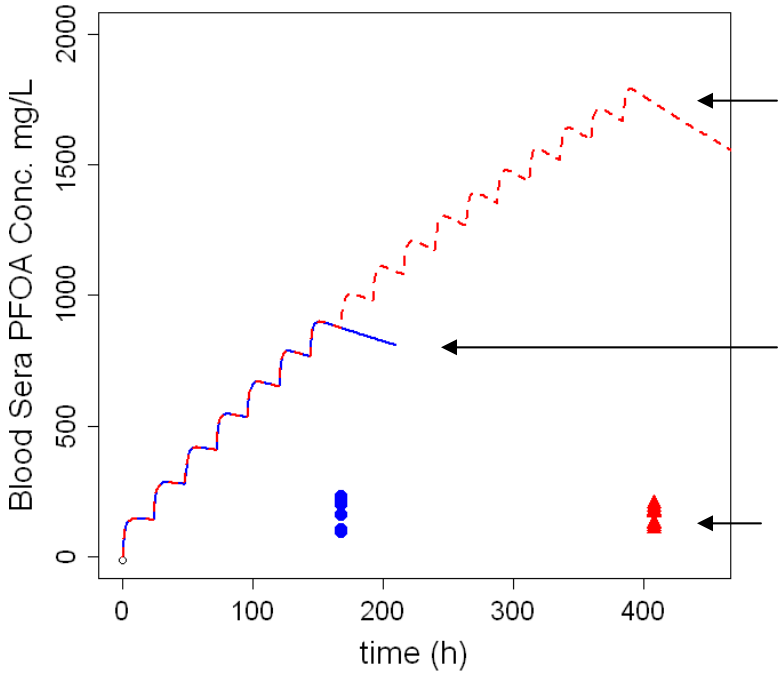
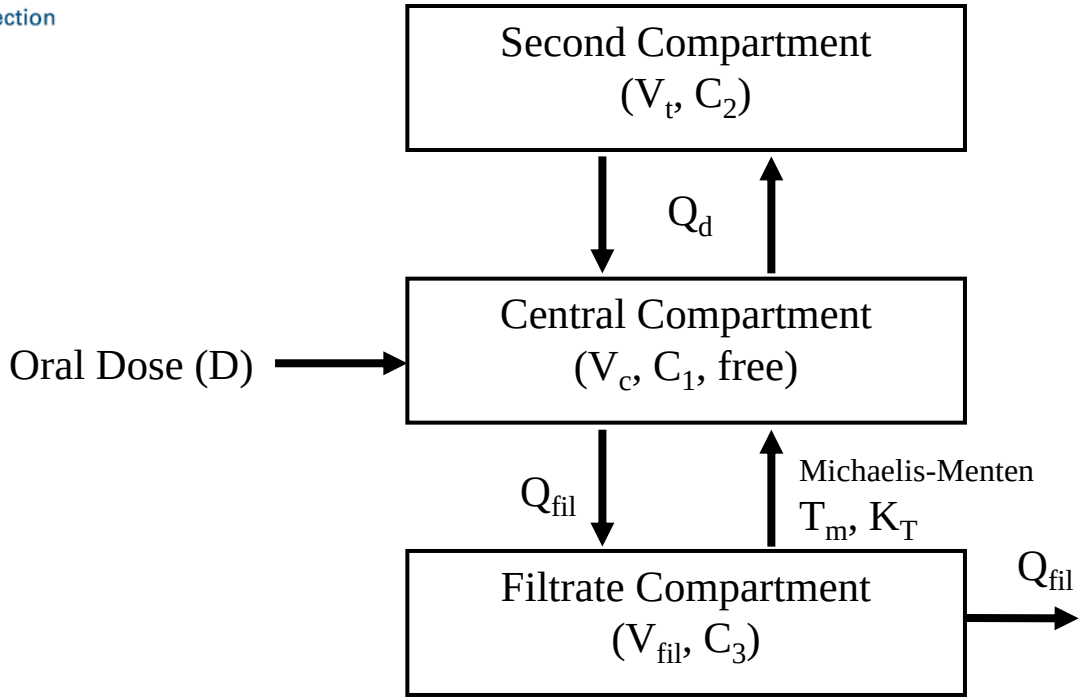
- PFOA has a human serum half-life of roughly four years
- Plasma half lives vary with species and sex: female rats (~4 hours), male rats (~4 days), and male and female monkeys (~1 month)
- Despite slow half-life, PFOA levels equilibrate rapidly in mice





The Saturable Resorption Model



Proposed by Andersen et al. (2006) for both PFOS and PFOA, based upon PFOA data that showed larger doses did not lead to larger serum concentrations

Possible mechanism is that saturable transporters (OATP1 and OAT3 – Katakura et al., 2007) recover the compounds from the filtrate before they are excreted (Ullrich et al., 1982)

Single and Repeated Doses Reconciled

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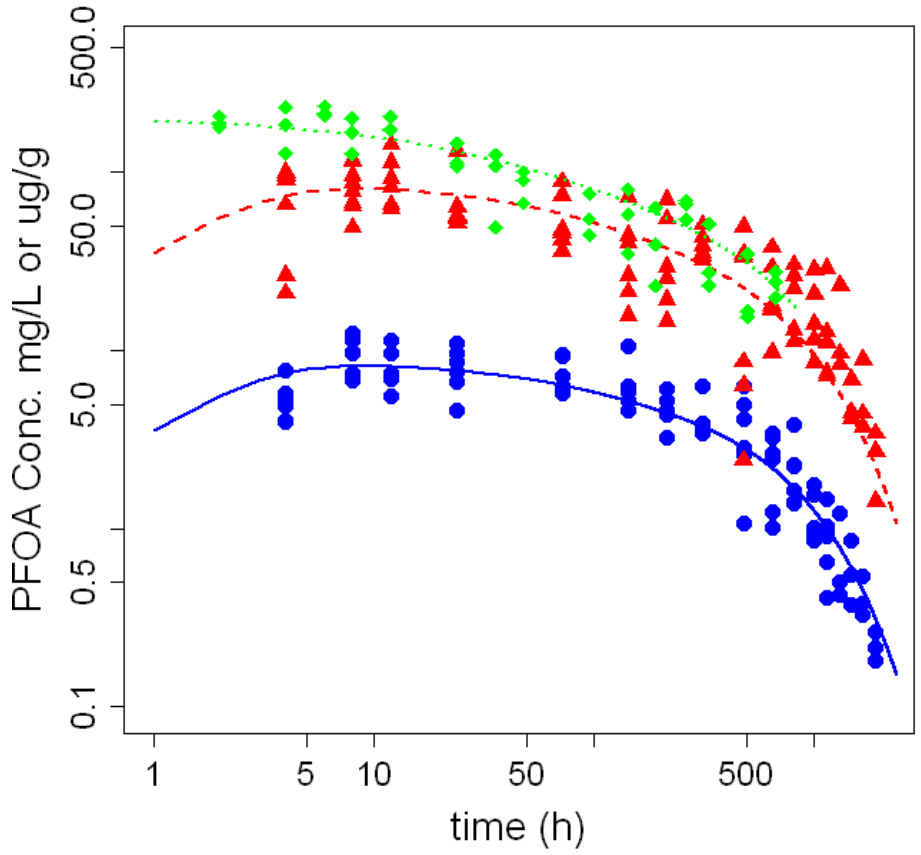
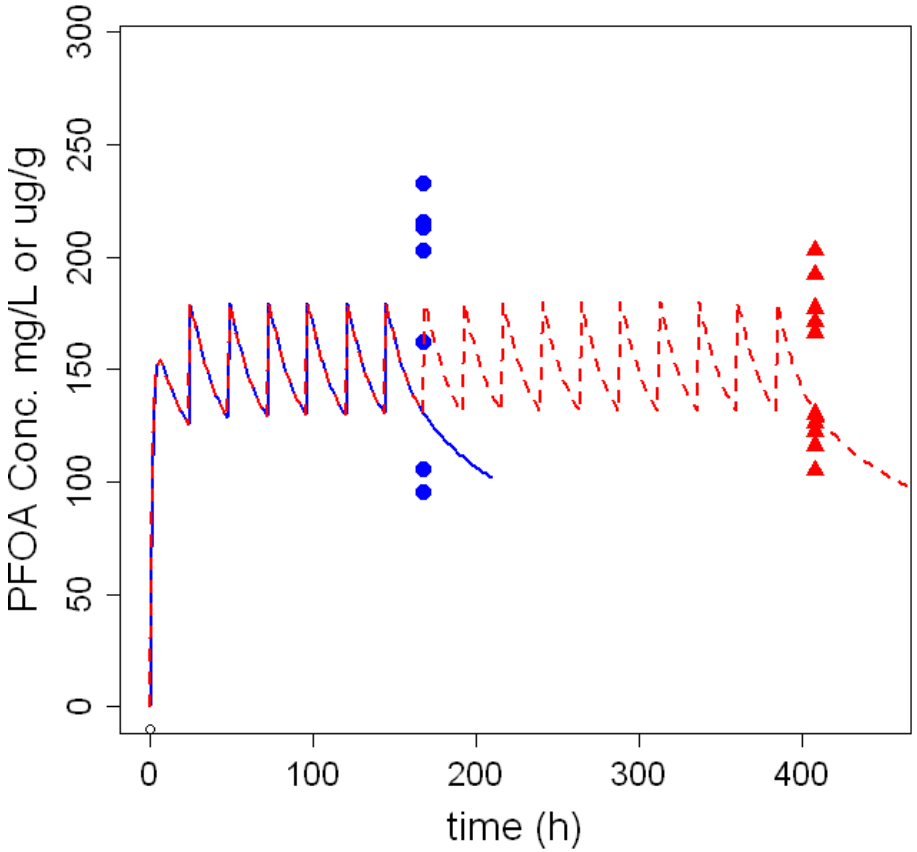
Female CD1 Mice

Single doses of 1, 10, 60 mg/kg

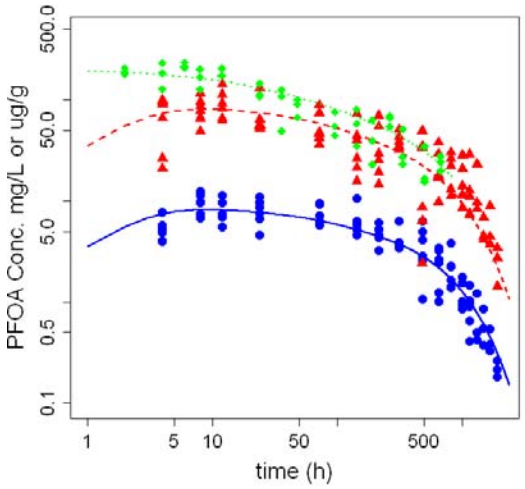


7- and 17-day repeat doses of 20 mg/kg



Lou et al. (2009)

Uncertainty in Parameter Estimates



		Mean	SD
V_{cc}	L/kgBW	0.1092	0.0080
k_{12}	1/h	0.2173	0.1351
k_{21}	1/h	0.0109	0.0075
V_{tc}	L/kgBW	2.1785	0.6059
Q_d	L/h	0.0006	0.0004
Q_{filc}	fraction	0.6346	0.9424
T_{mc}	mg/h/kgBW	94.0483	142.0120
K_T	mg/L	0.0015	0.0022

- V_t and Q_{fil} are very large
- Saturable transport parameters have large uncertainty
- Note that only 6 PK parameters were estimated – k_{12}, k_{21}, V_{tc}, and Q_d are not independent

Lou et al. (2009)

Bayesian Analysis of Dynamic Models

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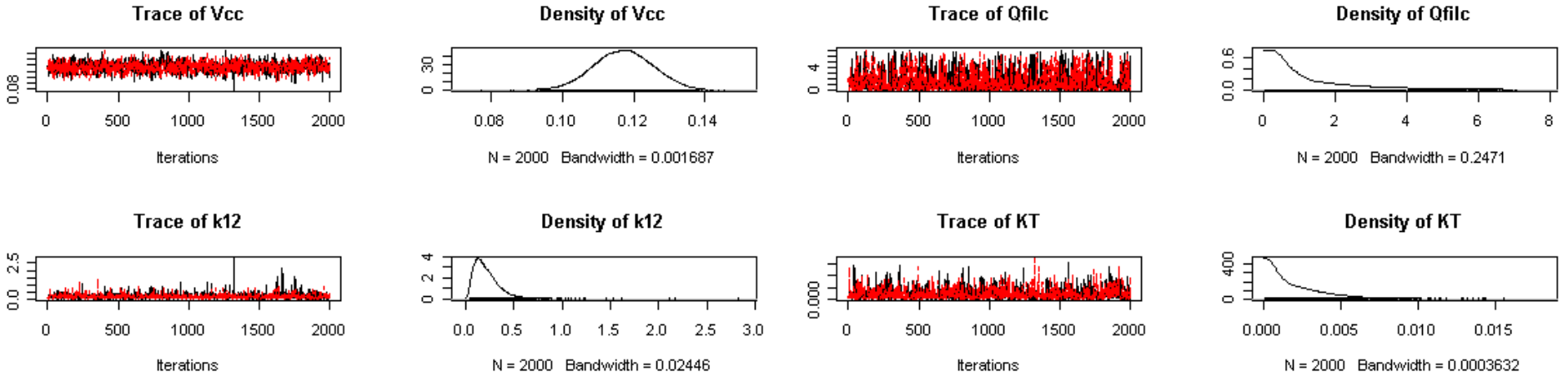
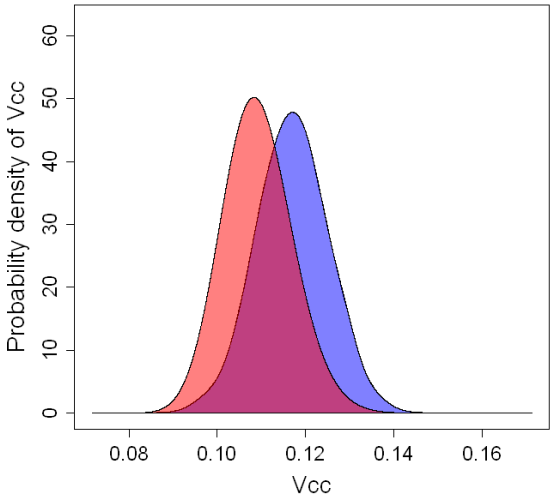
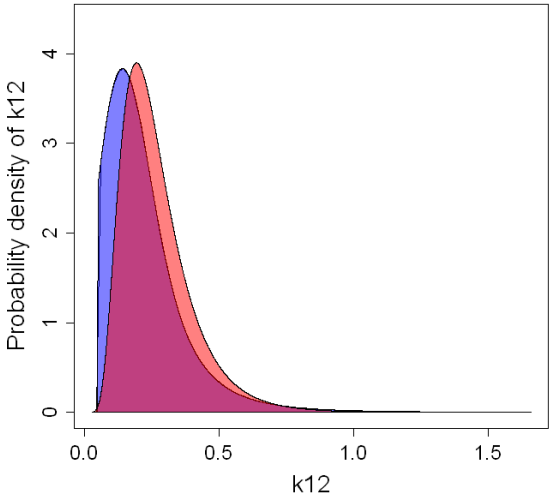
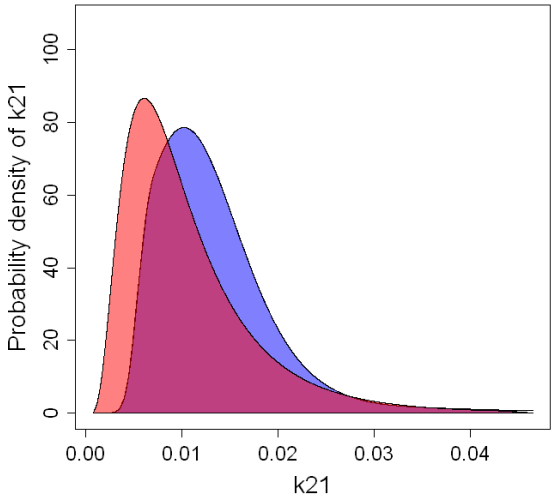
- Using MCMC sampler developed for R by Garcia, Wambaugh, Davis, and Setzer
- Analyzing a non-hierarchical model – single set of parameters to describe all animals
- Can use multiple data types/sources by estimating separate measurement variances
- Minimally informative priors on parameter values
- Can run several hundred thousand samples in a day on a desktop PC

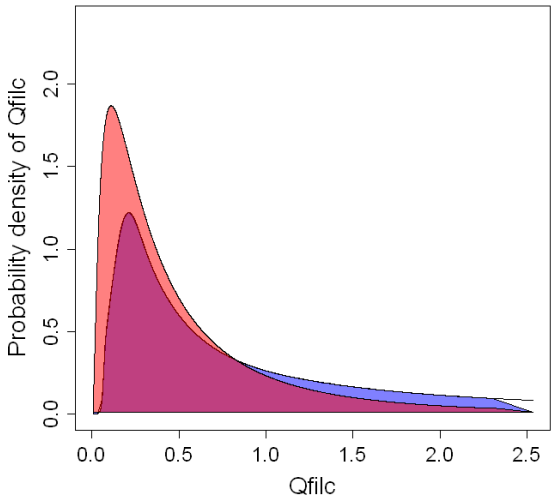


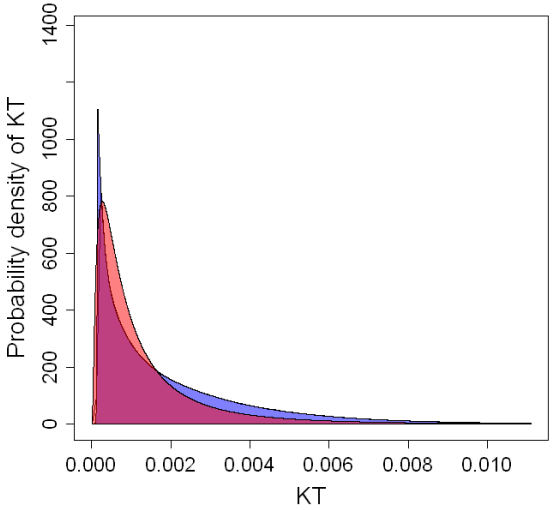
Bayesian Analysis of Saturable Resorption Model Parameters

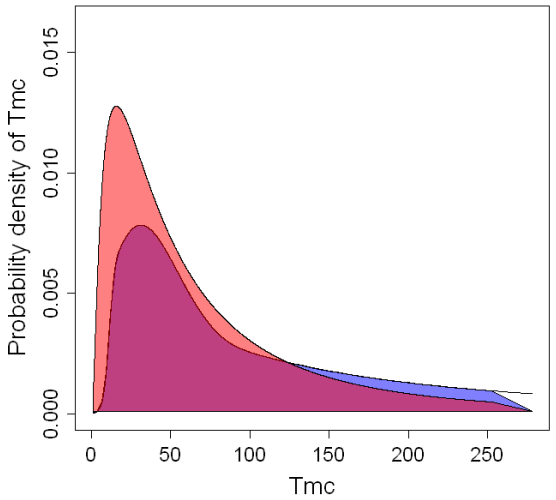












Bayesian Analysis

Lou et al. (2009) Maximum Likelihood

Accumulation in Liver of Male CD1 Mouse?

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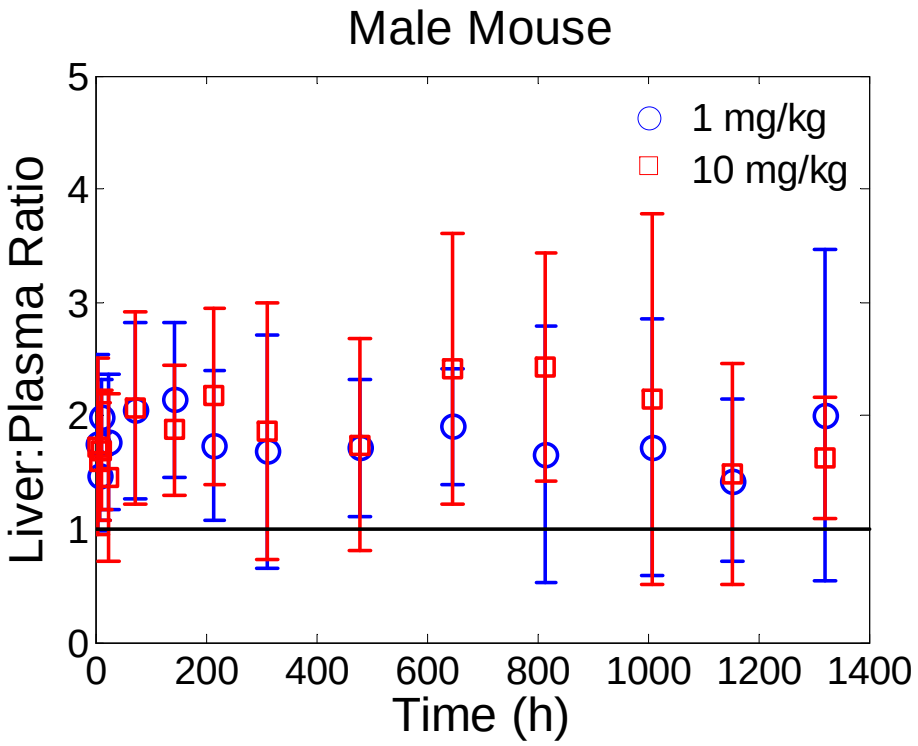
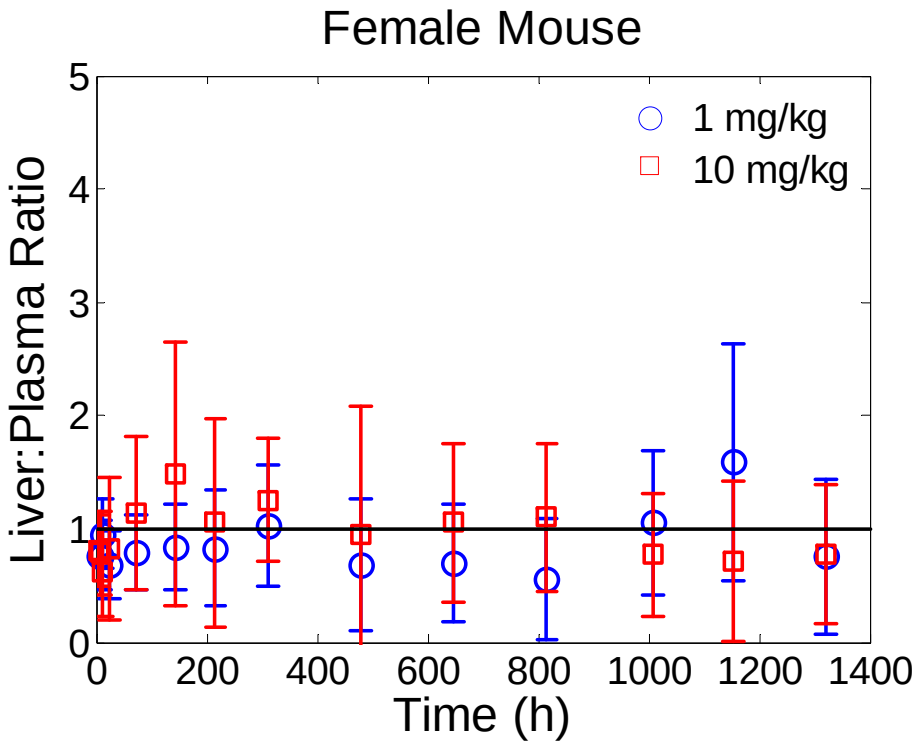
Single Dose





- Andersen et al. model explains serum, but not necessarily liver
- Evidence for sex-dependent distribution

Similar for Perfluorononanoic Acid (PFNA)?

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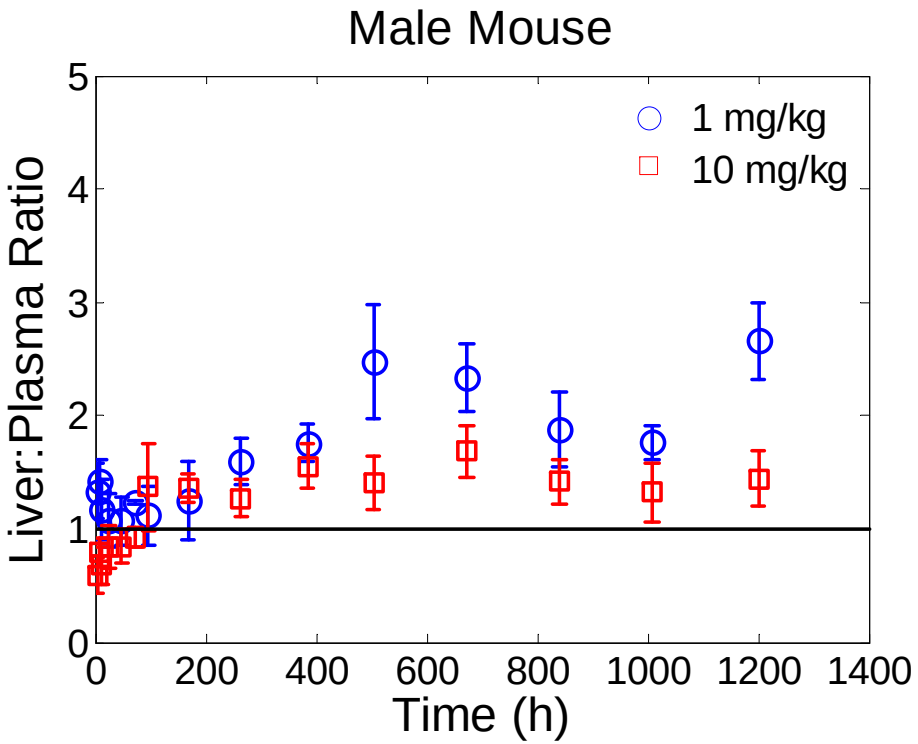
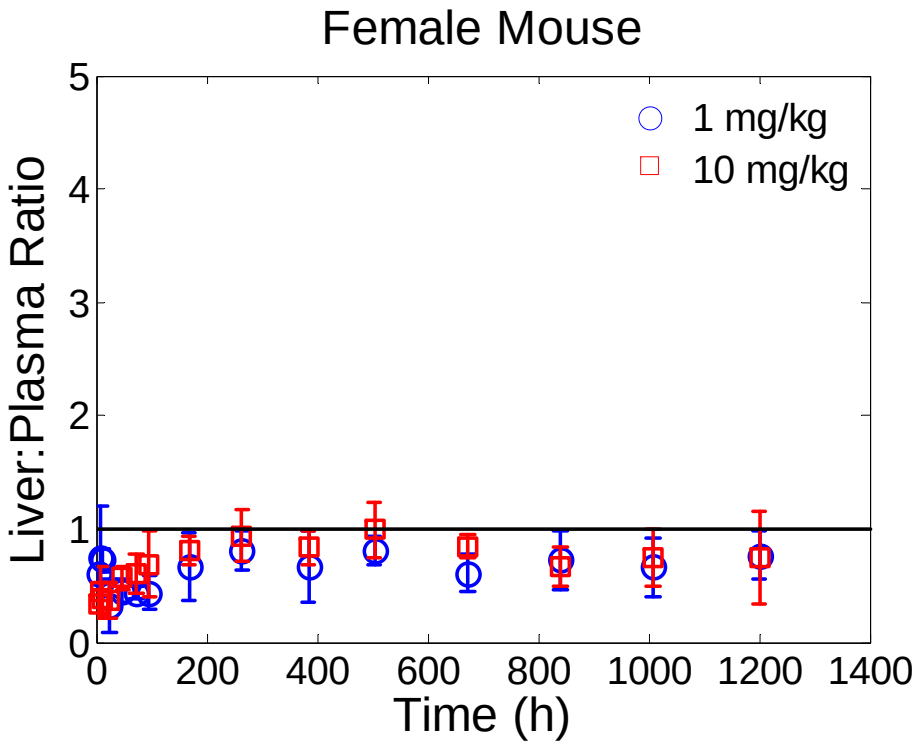
Single Dose





- Tatum et al. (Poster 505, Tuesday 9:00 AM)
- Gender difference may be general for moderate-length PFAA

Reconciling Male and Female PK

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- Male and female mice have roughly similar serum kinetics
  females: $t_{1/2}$ = 15.6 days, V_d = 0.135 L/kg
  males: $t_{1/2}$ = 21.7 days, V_d= 0.226 L/kg

- Different liver levels

- What explains the difference:

  - Offsetting differences in partitioning?

  - Different renal clearances (accumulation in filtrate)?

  - Differences in liver transporters (*e.g.* OAT, OATP)?

- If we want to include kidney and liver data from Lou et al. (2009) then we need a PBPK model

Physiologically-Based PK for PFOA

Physiologic Values:

Q_c, Q_l, Q_k, Q_{gf}, Q_{ur},
$Q_r = Q_c - Q_l - Q_k$

V_b, V_l, V_r, V_k, V_f

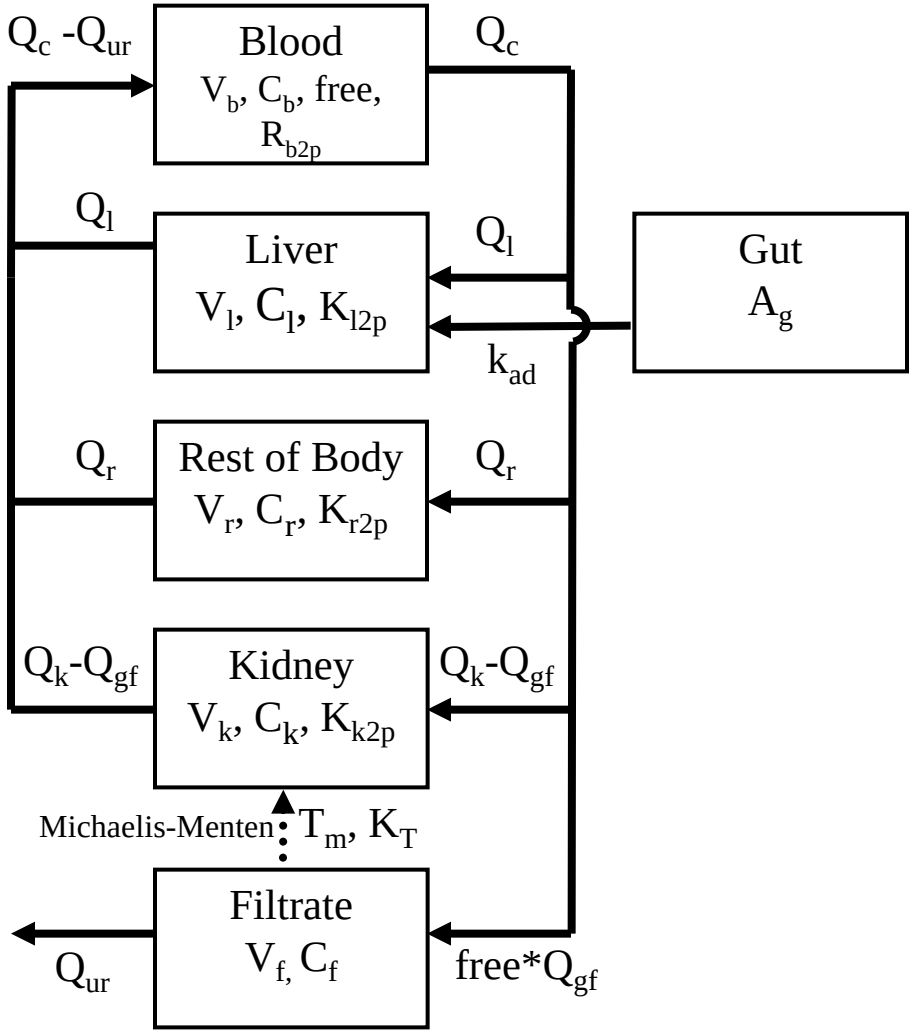
Assumed chemical specific values:

free = 0.02 (Andersen et al. (2006))
R_{b2p} = 0.48 (Ehresman et al. (2006))
k_{ad} = 1

Estimated values:

K_{l2p}, K_{r2p}, K_{k2p},
T_m, K_T,

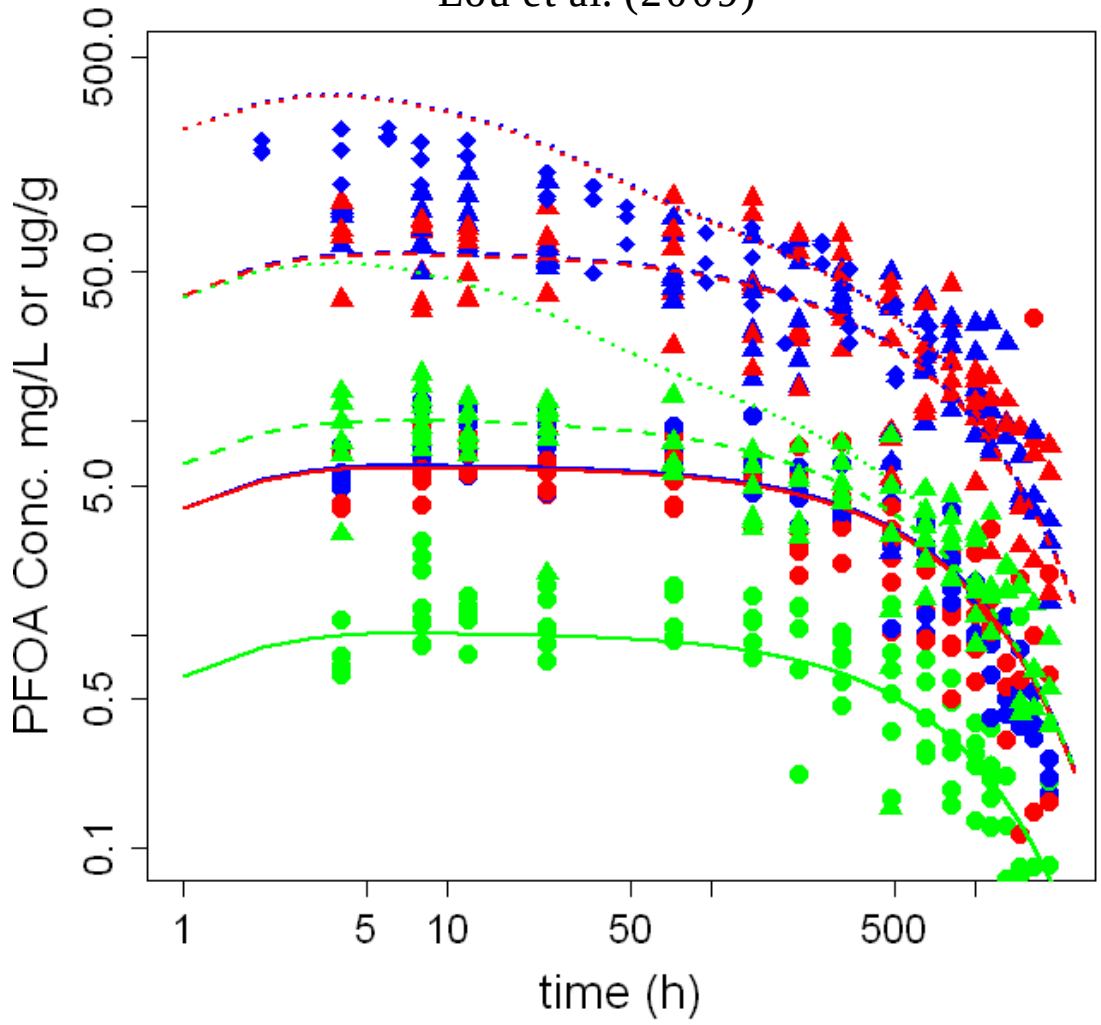
Kidney similar to Ethylene Glycol PBPK by Corley et al. (2000)



See also Rodriguez et al. (Poster 512, Tuesday, 9:00 am)

Tissue-specific Predictions

Single Dose 1 or 10 mg/kg
Lou et al. (2009)

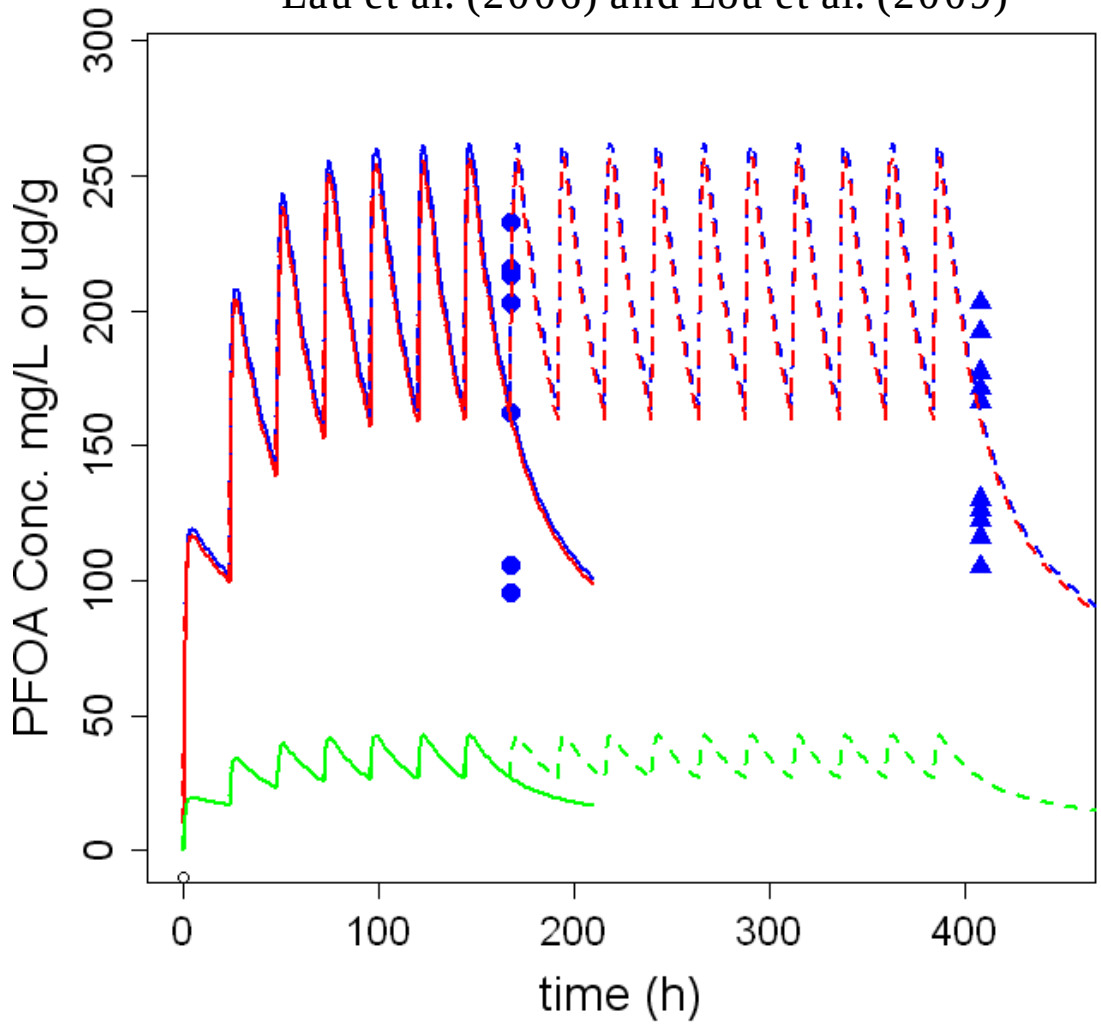


Blood Sera
Liver
Kidney

Tissue-specific Predictions

7- and 17-Day 20 mg/kg

Lau et al. (2006) and Lou et al. (2009)



Blood Sera
Liver
Kidney

Male Results

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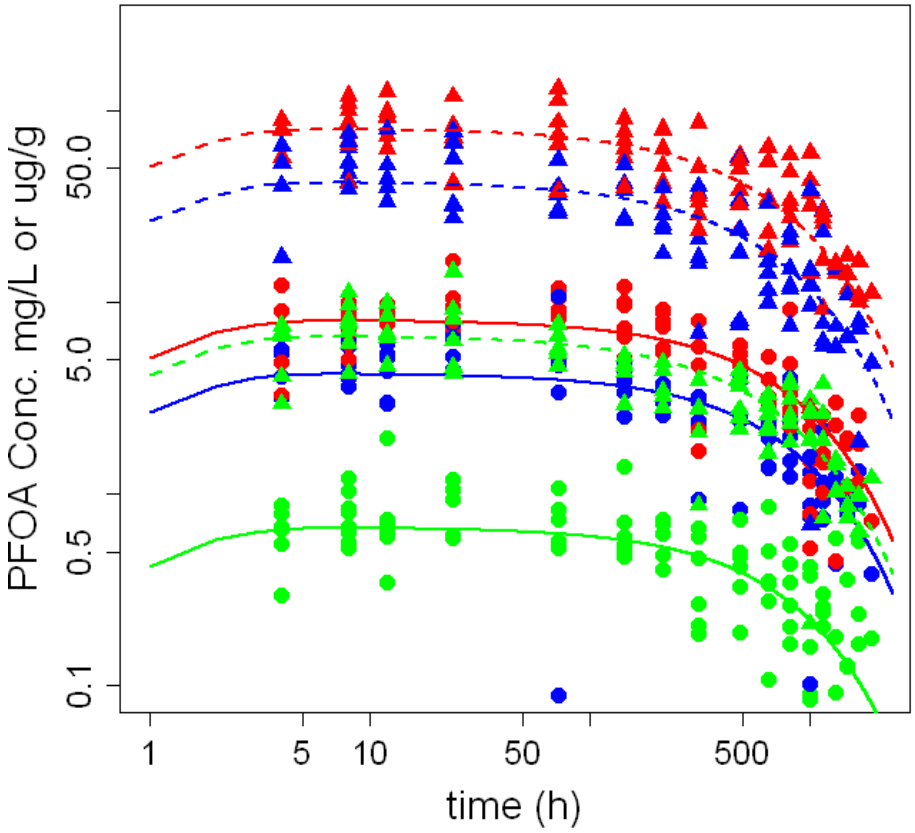
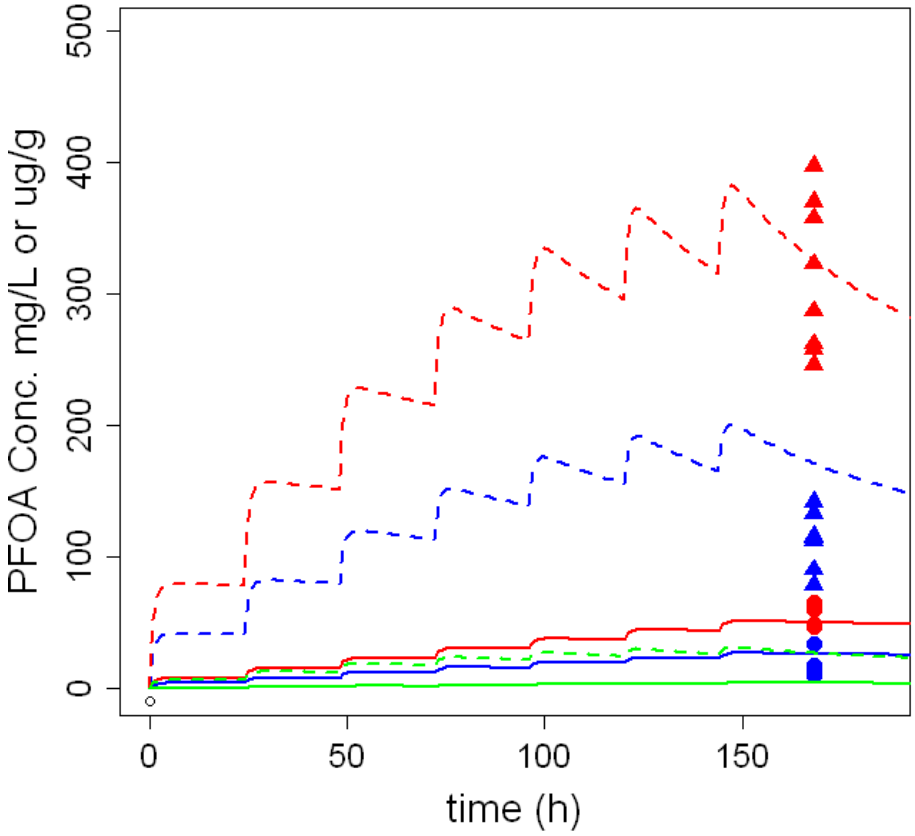
Single Dose 1 or 10 mg/kg
Lou et al. (2009)



7-Day 1 or 10 mg/kg
Wolf et al. (2008)



Blood Sera Liver Kidney

Gender Difference is in Distribution

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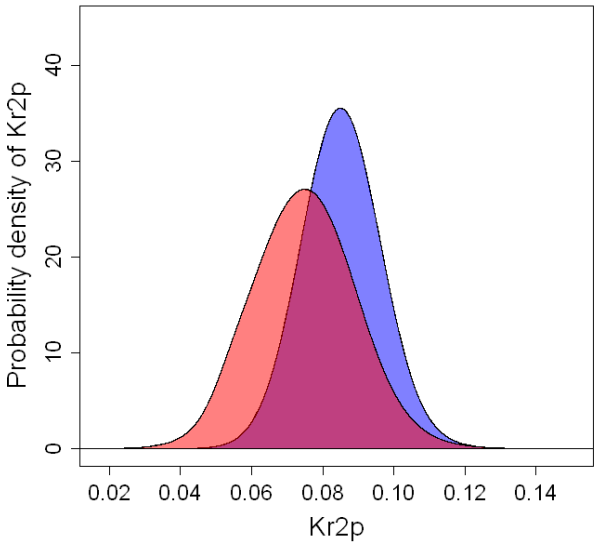
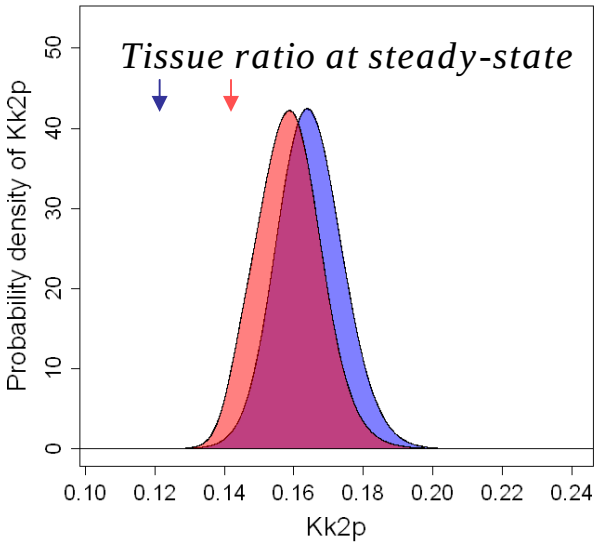
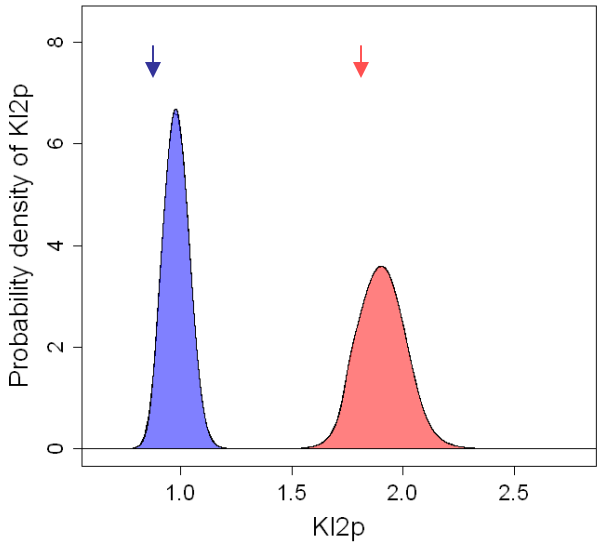
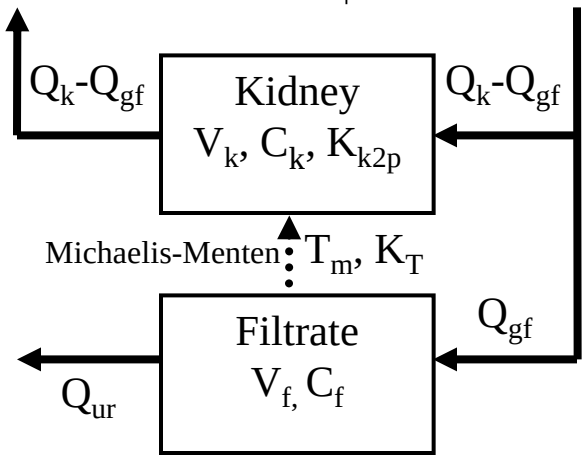
Female **Male**

Partition Coefficients

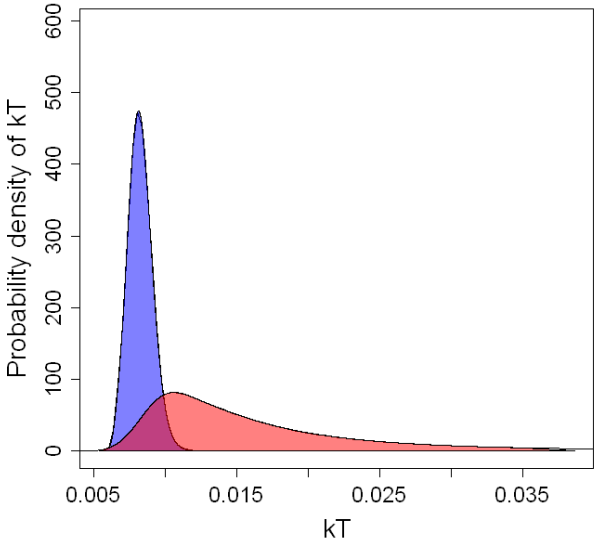


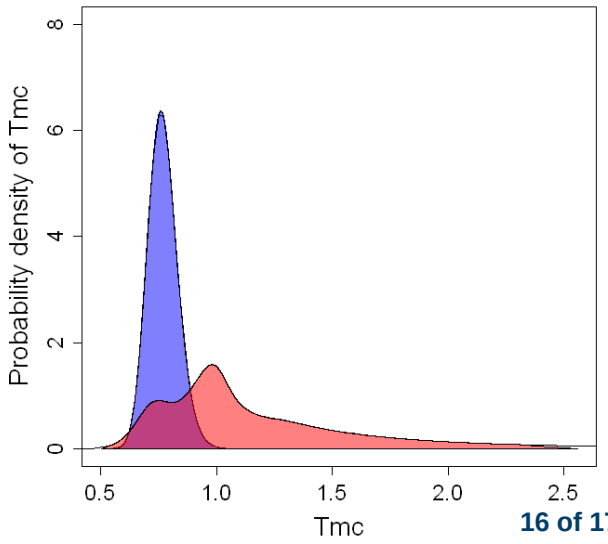






Saturable Renal Resorption





Future Directions

• Difference between CD1 mouse genders appears to be related to a process other than saturable resorption in the kidney

• Possible mechanisms include specific binding or transporter differences in the liver

• Additional complexity introduces additional parameters which must be estimated

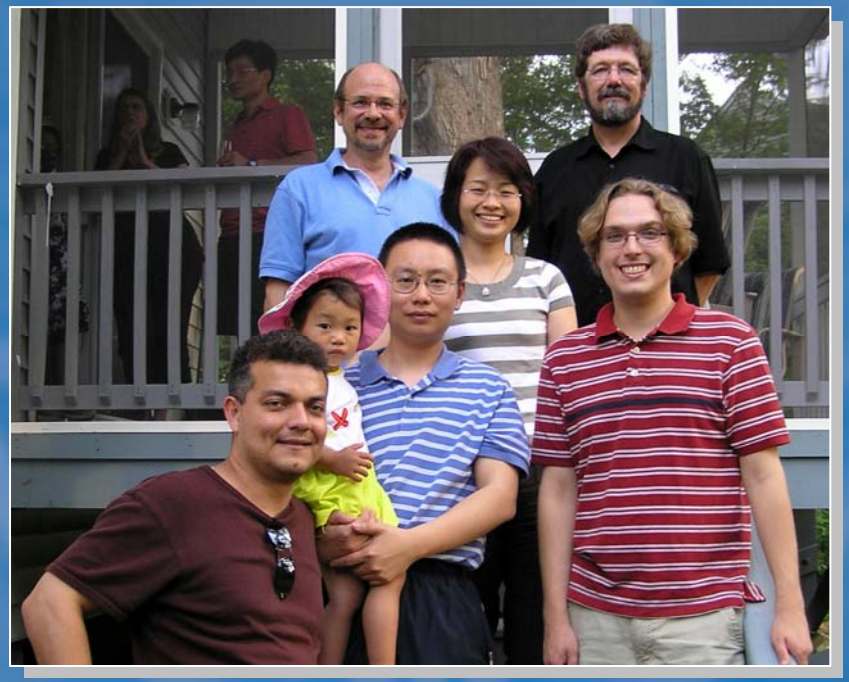
• Can discriminate between models using Bayesian Information Criterion (BIC) if comparing to the same data set

• PFAA is complicated

Acknowledgments

Thanks to the NCCT "statistics and PBPK group"!

Past
Hugh Barton
Inchio Lou
Miyoung Yoon



Current
Woody Setzer
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Dan Zehr
Katoria Tatum

National Exposure Research Laboratory
Andy Lindstrom
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