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PHARMACOKINETIC MODELING OF PERFLUOROALKYL ACIDS IN RODENTS

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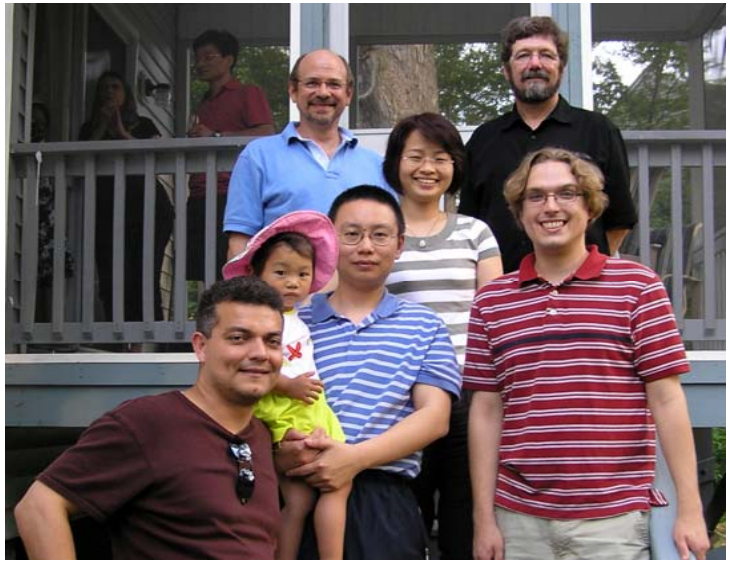

This presentation does not represent offical Agency policy.

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Outline

- Issues
- Classical PK Models for PFOA
- Saturable Reabsorption Model for PFOA
- Early Life Modeling
- Conclusions

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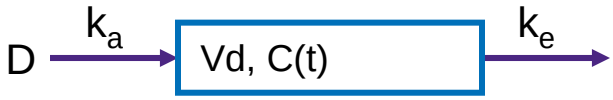
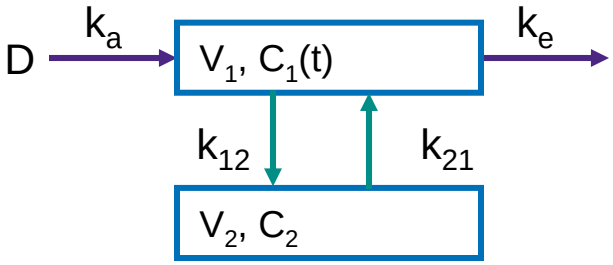
Classical Compartmental Analyses



- One and two compartment models with first order absorption and elimination
- Fitted by generalized nonlinear least squares

$$C(t) = \frac{k_a D}{(k_a - k_e)V_d}(e^{-k_e t} - e^{-k_a t})$$

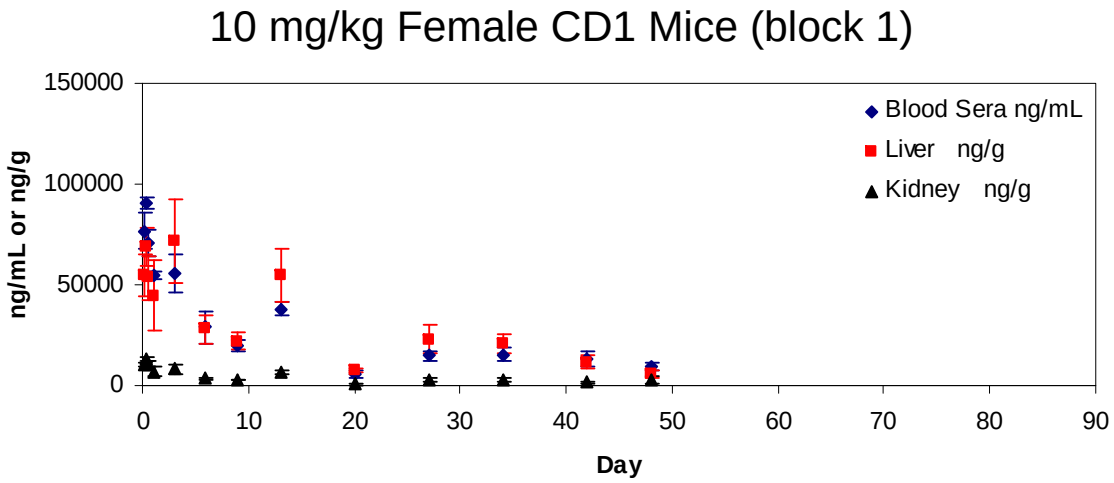


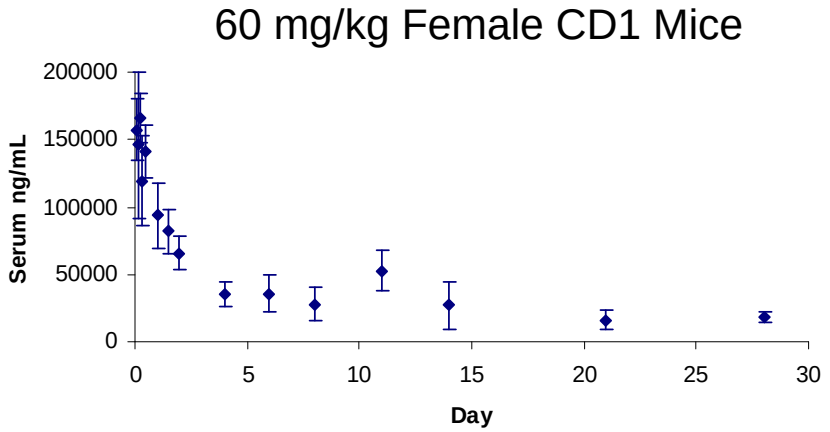
$$C(t) = \frac{k_a D}{V_1}\left[\left(\frac{k_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)}\right)e^{-\alpha t} + \left(\frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)}\right)e^{-\beta t} - \left(\frac{k_{21} - k_a}{(\alpha - k_a)(k_a - \beta)}\right)e^{-k_a t}\right]$$

α & β are complex functions of k_{12}, k_{21}, k_e

PFOA kinetic studies (aqueous gavage)

- Male & Female CD1 mice
- 1 & 10 mg/kg
- Serum, liver, kidney concentrations
- 60 mg/kg serum only in females only





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Parameter estimation summary after considering effects of gender, blocks and doses (1 & 10 mg/kg)

Vd: L/Kg; ka:h-1; ke:h-1			Female (95% confidence interval)	Male (95% confidence interval)
Blood Sera	V_d		0.135 (0.102-0.179)	0.226 (0.202-0.253)
	k_a		0.537 (0.300-0.960)	
	k_e		0.00185 (0.00175-0.00196)	0.00133 (0.00120-0.00148)
Liver	V_d		0.161 (0.148-0.176)	0.120 (0.111-0.129)
	k_a		0.517 (0.303-0.881)	
	k_e		0.00161 (0.00143-0.00181)	0.00129 (0.00115-0.00145)
Kidney	V_d	1 mg/Kg	0.822 (0.745-0.908)	1.280 (1.145-1.432)
		10 mg/Kg	1.092 (1.004-1.188)	1.700 (1.520-1.902)
	k_a		0.527	
	k_e		0.00151 (0.00138-0.00166)	0.00113 (0.000992-0.00128)

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Female Half Lives (One Compartment)

- Single Dose (1, 10 mg/kg/day)
  - Ke = 0.00185 h^{-1} T½ = 15.6 days
- Repeated Dosing (20 mg/kg/day aqueous gavage)
  - 176 ± 56 mg/L 24 hr after 7 days of dosing
  - 172 ± 34 mg/L 24 hr after 17 days of dosing
  - Ke = 0.0255 h^{-1} T ½ = 1.1 days
- T ½ appears concentration dependent

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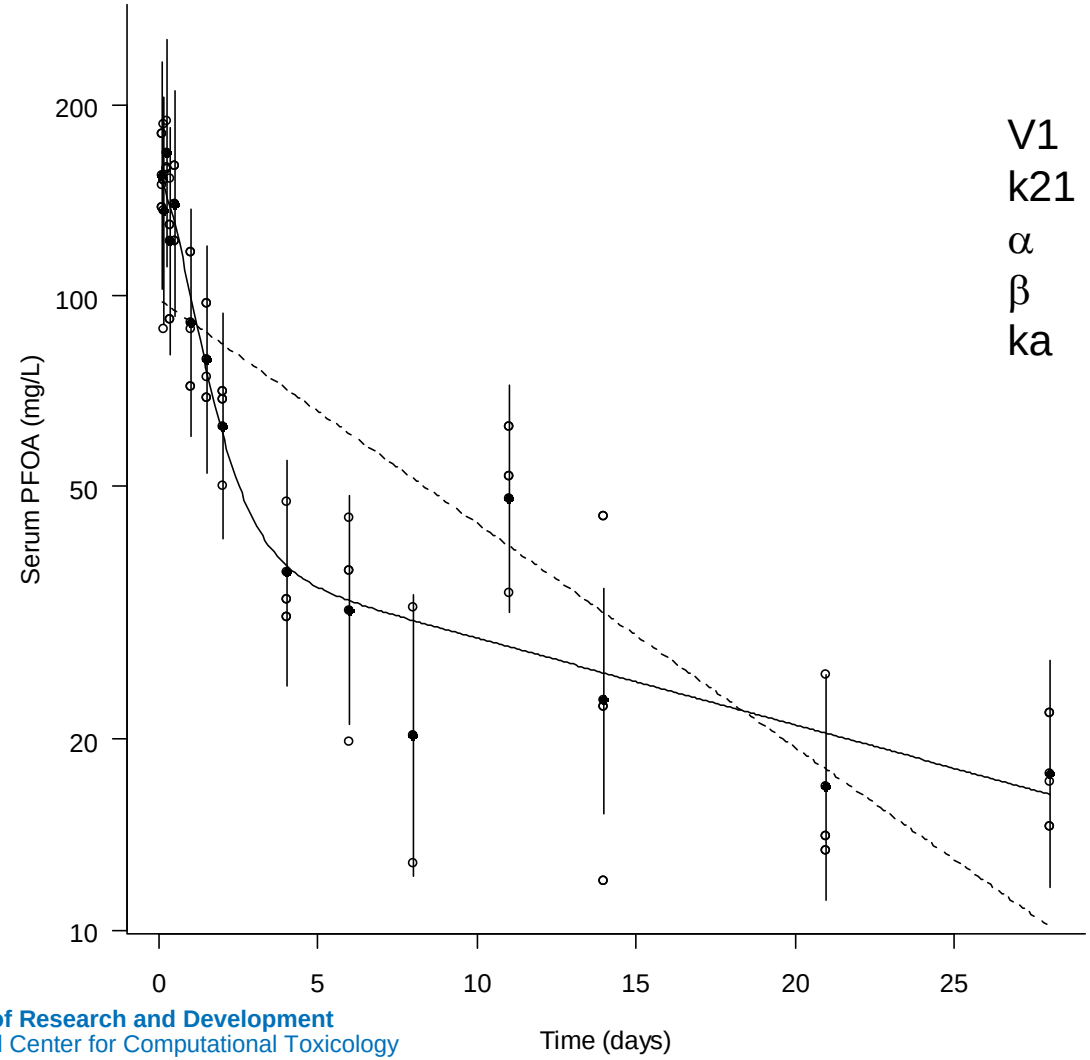
Two Compartment (60 mg/kg)



	estimated
V1	0.41
k21	0.0250
α	0.0917
β	0.00131
ka	0.0455

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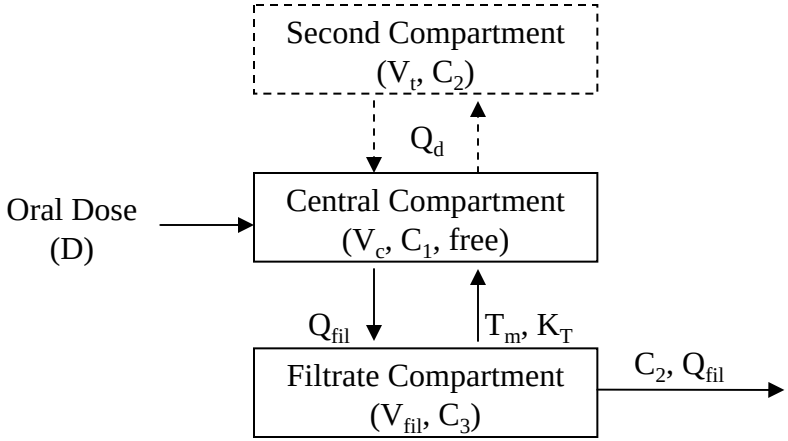
Saturable Reabsorption Model



- Maximum Likelihood Estimation

Andersen ME, Clewell HJ, Tan Y, Butenhoff JL and Olsen GW (2006), Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys – Probing the determinants of long plasma half-lives, 227: 156-164, Toxicology.

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Saturable Reabsorption Parameters

Parameter	Value (Standard Error)
Body Weight (BW)	25 g
Cardiac output	16.5 L/hr for mice
Absorption rate constant in the central compartment (k_a)	0.537 h^{-1} (*estimated from single dose data using one compartment model*)
Volume of distribution in the central compartment (V_c)	0.00326 (0.00015) L
Volume of renal filtrate (V_{fil})	0.01 L (*Andersen, et al., 2006*)
Renal blood filtrate rate (Q_{fil})	0.0258 (0.00086) L/h
Volume of distribution of second body compartment (Vt)	0.502 (0.934) L
Intercompartmental clearance	0.0000056 (0.0000005) L/h
Transport maximum (T_m)	0.117 (0.018) mg/h
Transport affinity constant (K_T)	0.001 (0.0007) mg/L
Proportion of PFOA free in serum (free)	0.06 (0.015)

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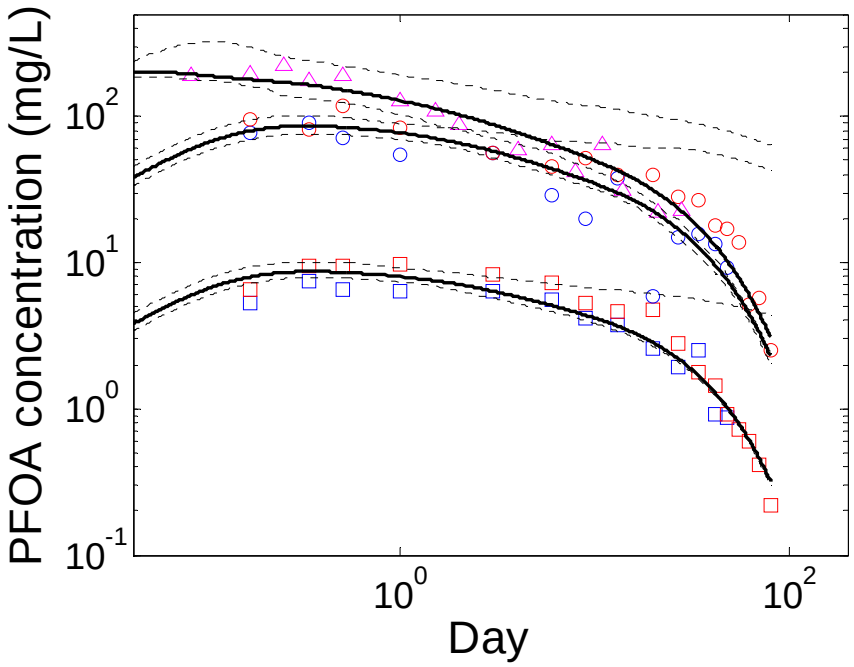
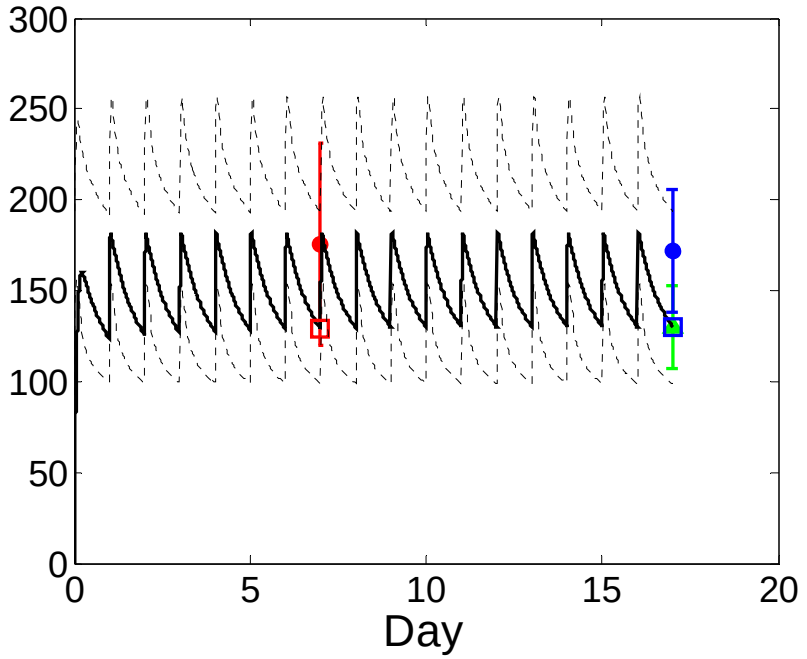
Saturable Reabsorption Simulations

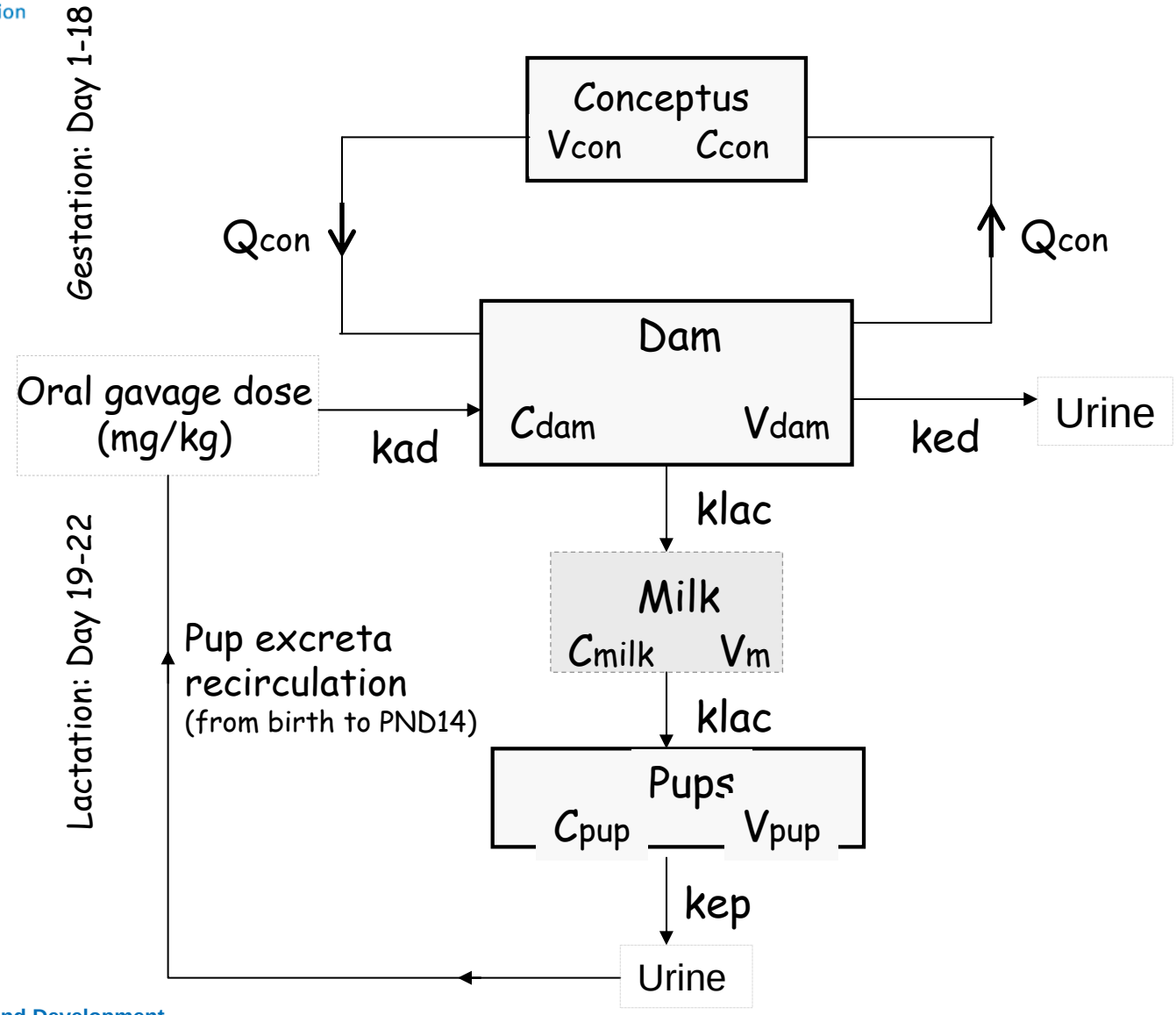
Single Doses (1, 10, 60 mg/kg)



Repeated Doses (20 mg/kg, 7 & 17 days)



Linear Pregnancy/Lactation Model



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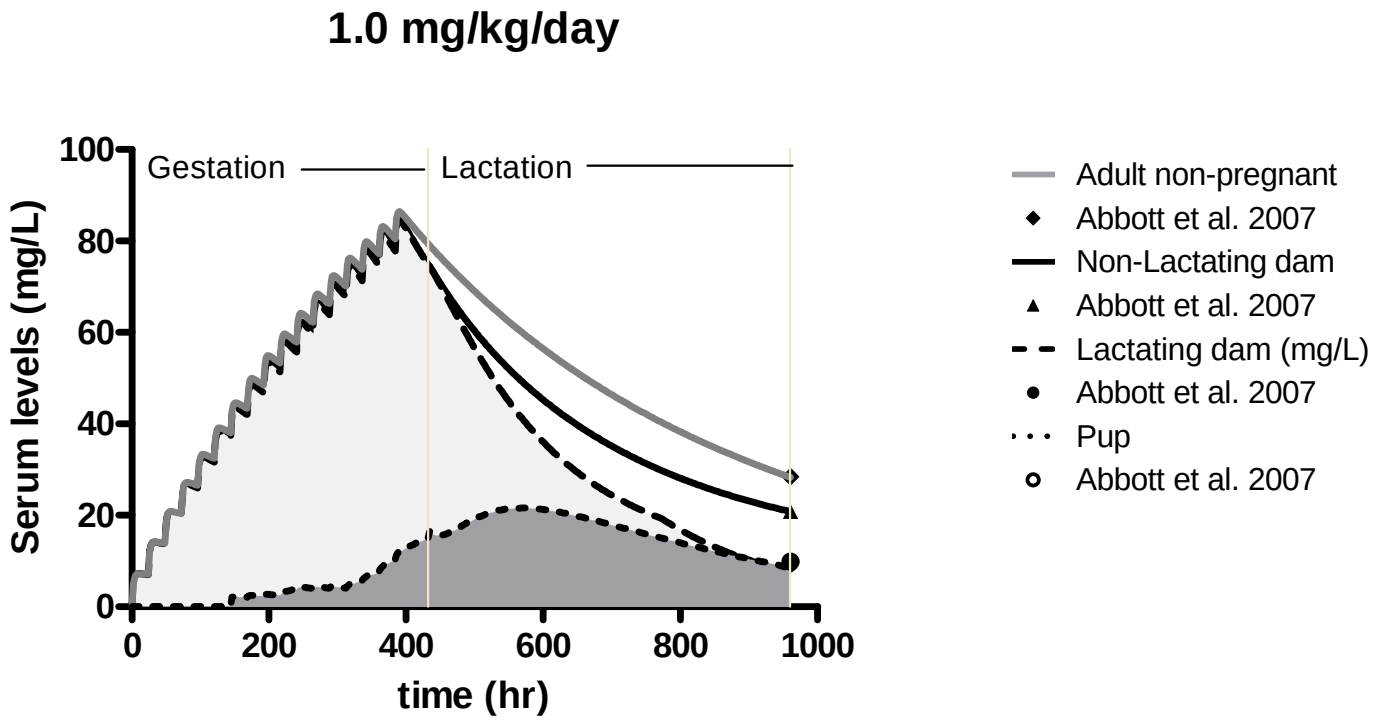
Non-pregnant, pregnant, lactating 129 mouse dam & offspring



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Conclusions

- Male and female mice similar distribution and clearance at 1 and 10 mg/kg following single oral dose
- One compartment model appropriate for 1 and 10 mg/kg data, but two compartment required for 60 mg/kg
- Concentration dependent changes in distribution and clearance
- Saturable reabsorption plausibly explains data
- Early life modeling ongoing

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Unresolved Issues

- Mouse strain PK differences – CD1 & 129J
- Time- & concentration-dependent changes in biliary excretion, liver tissue distribution, urinary clearance – impacts of saturable processes, age, chemical?
- Saturable reabsorption? No direct urinary excretion data.
- Quantification – tissue processing and analytical chemistry can be reproducible, but can also result in substantial differences. Comparisons across experiments and laboratories require caution.