PHARMACOKINETIC MODELING OF PERFLUOROOCTANOIC ACID DURING GESTATION AND LACTATION IN MICE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY — COMPUTATIONAL TOXICOLOGY

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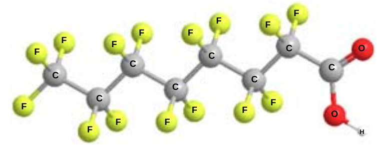


PFOA

INTRODUCTION

- A fully fluorinated alkyl acid used as a surfactant for the polymerization of fluoropolymers such as polytetrafluoroethylene (Teflon ®)
- Non-biodegradable and persistent in the environment; C-F bond is too strong for biological systems to cleave
- Widely detected in human serum samples at low ppb for the general US population to low ppm for occupationally exposed workers and other highly exposed populations
- Developmental toxicity in rodents identified as one of the most sensitive adverse effects

F1 generation

Rat — **30 mg/kg/day** →
- Pre-/post-weaning body weight deficits
- Increased post-weaning mortality
- Delays in sexual maturation

(1)

Mice

5 mg/kg/day ↑ **0.1 mg/kg/day**

Neonatal	**Maternal**
Neonatal lethality	Loss of pregnancy
Mammary gland alterations	Body weight deficit
Eye opening delay	Mammary gland alterations
Body weight deficits	Parturition time delay
Liver hypertrophy	Liver hypertrophy

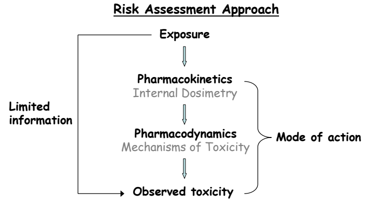
(2, 3, 4, 5)

- Found at low ppb levels in human samples of umbilical cord blood, neonatal blood collected immediately after birth, and breast milk
- Serum/plasma clearance varies dramatically across species (and gender)

Half-life estimates:
- humans: 3-5 years
- monkeys: 21-30 days
- mice: 12-20 days
- male rat: 4-6 days
- female rat: 2-4 hrs

(6)

Risk Assessment Approach



RESEARCH GOALS

- To explore possibilities in model structure that can be supported by serum information from developmental toxicity studies in the mouse
- To provide estimates of internal dose metrics for dam and offspring during gestation and lactation
- To compare internal dose estimates to those reported for the rat as a means for addressing differences in plasma clearance in these two species

METHODS AND APPROACH

Absorption was described as first order process for all pregnant mice using a rate constant of 0.537 /hr estimated for adult non-pregnant CD-1 mice (7). Elimination was modeled as first order for 129 S1/SvlmJ mice using a rate constant estimated from serum measurements reported in non-lactating mice (2). A volume of distribution of 0.135 L/kg BW estimated for adult non-pregnant CD-1 mice (7) was assumed to apply to all mice including concepti and nursing pups.

Gestation

Gestation was described as a two-compartment system (dam + concepti) linked via placental blood flow (Qcon). The growth of the concepti compartment was estimated as the difference between total pregnant female BW and the predicted contribution of maternal tissues (mammary, liver, uterus, and carcass fat) (8). A previously published mathematical expression was used to describe the development of placental blood flow (8) but adjusting for the timing of gestation specific for the mouse (a full 18-day period). Embryo/fetus:maternal plasma partition coefficients for PFOA as a function of gestation day were estimated from (9).

Lactation

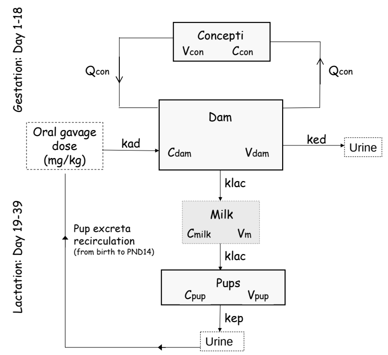
Lactation was described as dam and pup litter compartments linked via milk production. It was assumed that the pups consumed all the milk produced without delay. Milk yield information as a function of lactation day was taken from (10), expressed on a per pup basis, and fitted to a cubic expression (Graphpad Prism). Body weight (BW) increases for the lactating mouse dam were taken from (11), fitted to a 2nd order polynomial (Graphpad prism), and linked correspondingly to the predicted BW for the pregnant dam (excluding concepti) at the end of gestation as described above. Similarly, BW increases for the pup were taken from (2, 3), fitted to a 2nd order polynomial (Graphpad prism), and linked correspondingly to the predicted birthweight. The milk:maternal plasma partition coefficient was fitted to a value of 0.028 and assumed constant throughout lactation

Renal Resorption Component

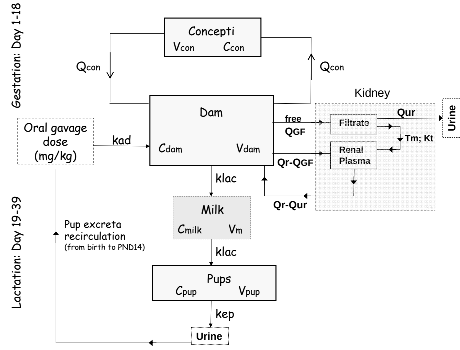
The kidney resorption component was adapted from (12). The Glomerular filtration rate (GFR) was taken from (13) The volumes of the filtrate and renal plasma compartments were estimated by BW scaling of values reported for the dog (12). Transport affinity constant (Kt) and transport maximum (Tm) were estimated using maternal serum levels of PFOA reported at term (2). The same value of Kt was assumed for simulating postnatal serum measurements. Urine flow rate (Qur) was taken from (14).

RESULTS

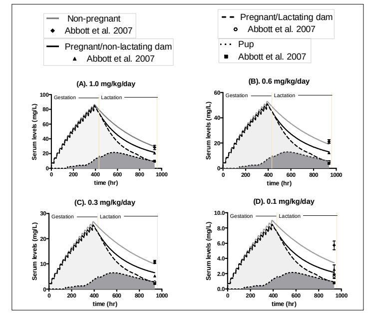
Model used in the analysis of 129S1/SvlmJ mice



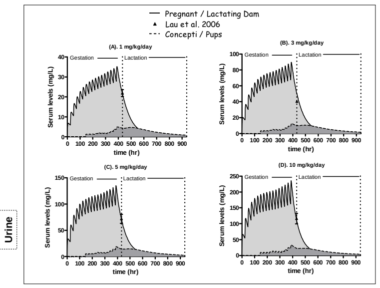
Model used in the analysis of CD-1 mice



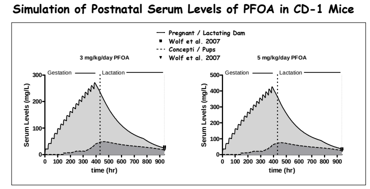
Simulation of Serum Levels of PFOA in 129 S1/SvlmJ Mice



Simulation of Prenatal Serum Levels of PFOA in CD-1 Mice



Simulation of Postnatal Serum Levels of PFOA in CD-1 Mice



Estimates of internal dose metrics for developmental toxicity studies in rodents

Dose (mg/kg/day)	Species (strain)	Life stage	Toxic effect	NOAEL or LOAEL	Reference	AUC average daily ((mg/L)*hr) G	AUC average daily ((mg/L)*hr) G +L	C_{max} (mg/L)	t_{max} (hr)
0.1	Mouse (129S1/SvlmJ)	Dam	None	-	[21]	118	94	8	390
		Pups	Liver hypertrophy	LOAEL	[21]	14	25	2	498
0.3	Mouse (129S1/SvlmJ)	Dam	None	-	[21]	355	283	25	390
		Pups	Liver hypertrophy Neonatal lethality	- NOAEL	[21]	41	76	7	498
0.6	Mouse (129S1/SvlmJ)	Dam	Liver hypertrophy	NOAEL	[21]	711	566	49	390
		Pups	Liver hypertrophy Neonatal lethality Neonatal BW deficit Eye opening delay	- LOAEL NOAEL NOAEL	[21]	82	153	14	498
1.0	Mouse (129S1/SvlmJ)	Dam	Liver hypertrophy	LOAEL	[21]	1185	943	82	390
		Pups	Liver hypertrophy Neonatal lethality Neonatal BW deficit Eye opening delay	- - LOAEL LOAEL	[21]	137	254	24	498
1.0	Mouse (CD-1)	Dam	Liver hypertrophy Parturition delay	LOAEL NOAEL	[22]	548	296	34	388
		Pups	Neonatal BW deficit Eye opening delay	LOAEL LOAEL	[22]	55	48	5	390
3.0	Rat (Sprague Dawley)	Dam	None	-	Draft risk assessment	83		13	2
		Pups	Neonatal BW deficit Post-weaning lethality Sexual maturation delay Post-weaning BW deficits	NOAEL NOAEL NOAEL NOAEL	Draft risk assessment	Not available			

CONCLUSIONS

- A two-compartment model supported with biological information provided a good initial template to investigate the pharmacokinetics of PFOA in mouse developmental toxicity studies.
- Different descriptions of clearance were necessary to simulate serum levels from two different strains: a linear description was sufficient for 129S1/SvImJ mice at doses of ≤ 1 mg/kg/day, whereas saturable renal resorption allowed simulation of serum levels in CD-1 mice at doses ≥ 1 mg/kg/day.
- An unexplained discrepancy was noted for CD-1 mice: simulation of prenatal and postnatal serum measurements were found to differ in their predicted prenatal profiles.
- Although mice may appear more sensitive based on administered dose of PFOA, this analysis indicates that mice may be equal or less sensitive than rats when considering internal dose metrics.

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REFERENCES

(1). Butenhoff JL, Kennedy GL, Jr., Frame SR, O'Connor JC, York RG. Toxicology. 2004, 196(1-2):95-116
(2). Abbott BD, Wolf CJ, Schmid JE, Das KP, Zehr RD, Helfant L, et al. Toxicol Sci. 2007, 98(2):571-81.
(3). Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, et al. Toxicol Sci. 2006, 90(2):510-8.
(4). Wolf CJ, Fenton SE, Schmid JE, Calafat AM, Kuklenyik Z, Bryant XA, et al. Toxicol Sci. 2007, 95(2):462-73
(5). White SS, Calafat AM, Kuklenyik Z, Villanueva L, Zehr RD, Helfant L, et al. Toxicol Sci. 2007, 96(1):133-44
(6). Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. Toxicol Sci. 2007, 99(2), 366-94
(7). Lou I, Wambaugh JF, Lau C, Hanson RG, Lindstrom AB, Strynar MJ, et al. Toxicol Sci. 2009, 107(2):331-41
(8). O'Flaherty EJ, Scott W, Schreiner C, Beliles RP. Toxicol Appl Pharmacol. 1992, 112(2):245-56
(9). Henderson WM, Smith MA. Toxicol Sci. 2007 95(2):452-61.
(10). Knight CH, Maltz E, Docherty AH. Comp Biochem Physiol A Comp Physiol. 1986, 84(1):127-33
(11). Johnson, M. S. and J. R. Speakman. J Exp Biol 2001, 204(Pt 11): 1967-77.
(12). Russel, F. G., A. C. Wouterse, et al. Biopharm Drug Dispos. 1989 10(2), 137-52.
(13). Qi, Z., I. Whitt, et al. Am J Physiol Renal Physiol 2004 286(3), F590-6.
(14). Meneton, P., I. Ichikawa, et al. Am J Physiol Renal Physiol 2000 278(3): F339-51.

This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.