MODELING THE PHARMACOKINETICS OF PERFLUOROOCTANOIC ACID DURING GESTATION AND LACTATION IN MICE

Chester E. Rodriguez and Hugh A. Barton
National Center for Computational Toxicology, U.S. EPA, RTP, NC

research&development

Science Question

Perfluorooctanoic Acid (PFOA)

• A fully fluorinated alkyl acid which has been widely used as a surfactant and emulsifier for the production of commercially valuable fluoropolymers and fluoroelastomers.

• The carbon-fluorine bonds give exceptional stability and inertness which are ideal properties for its commercial applications, but make it practically non-biodegradable and persistent in the environment.

• Widely detected in human serum samples where levels can range between low parts per billion for the general US population to low parts per million for occupationally exposed workers and other highly exposed populations.

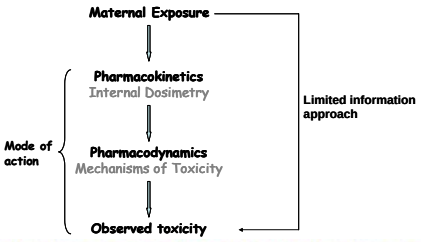
• Exhibits relatively long plasma half-lives (human plasma half-life estimated at ~3-5 years) and clearance can vary dramatically across species, and for some species, across gender.

• Induces developmental toxicity in mice in the form of full-litter resorption, compromised postnatal survival, delayed growth and development, and altered pubertal maturation.

• It remains to be delineated whether the observed developmental toxicity results from pharmacokinetic changes (higher internal dose) and/or exposure during developmentally sensitive periods.

• Risk analysis may be greatly improved with pharmacokinetic models that quantitatively describe the pharmacokinetic changes associated with one-generation toxicity studies.

Risk Assessment Approach



Research Goals

• To develop an initial biologically-supported pharmacokinetic model for describing exposure of PFOA during gestation and lactation in the mouse.

• To compare how such a model may differ from that of an adult non-pregnant mouse.

• To assess the relative contributions of gestational versus lactational exposure to pups.

Methods/Approach

Absorption and elimination were described as first order processes. An absorption rate constant estimated for the adult mouse (1) was assumed to be the same at all modeled life stages. All of the serum data used to calibrate and evaluate the model predictions were from the 129S1SvlmJ mouse strain (2).

Gestation

Gestation was described as a two-compartment (dam + conceptus) system linked via placental blood flow (Qcon). The conceptus was made up of the embryo/fetus and placenta. Mathematical expressions describing the growth of the dam, embryo/fetus, placenta, and Qcon were taken from (3) and adjusted for the timing of gestation specific for the mouse (a full 18-day period). In the case of the embryo/fetus, mathematical expressions describing growth were modified to fit reported maternal weight gain data (4). Embryo/fetus:maternal plasma partition coefficients for PFOA as a function of gestation day were estimated from (5). The elimination rate constant for the dam and nursing pups were obtained by optimization using non-lactating dam serum data (2), followed by allometrically-scaling.

Lactation

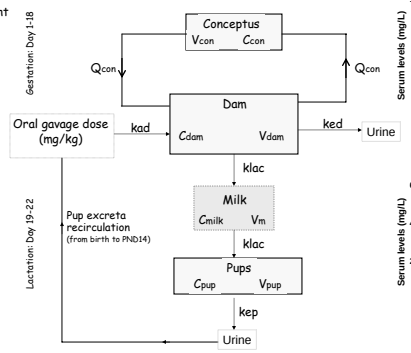
Lactation was described as a dam and pup litter compartment linked via milk production. It was assumed that the pups consumed all the milk produced without delay. Milk yield information as a function of lactation day was taken from (6), expressed on a per pup basis, and fitted to a one-site binding hyperbola (Graphpad prism). Body weight (BW) increases for the lactating mouse dam were taken from (7), fitted to a 2nd order polynomial(Graphpad prism), and linked correspondingly to the predicted BW for the pregnant dam (excluding conceptus) at the end of gestation as described above. Similarly, BW increases for the pup were taken from (4), 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 0.04 and assumed constant throughout lactation

Adult mouse

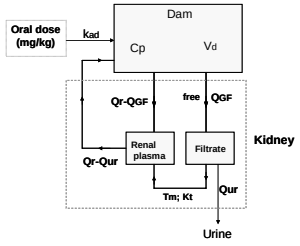
A constant BW of 25 g was used for the adult mouse. The kidney resorption component was adapted from (8). The Glomerular filtration rate (GFR) was taken from (9) The volumes of the filtrate and renal plasma compartments were optimized using serum levels of mice whose litters were fully resorbed early in pregnancy, and thus can be considered as adult non-pregnant mice (2). Urine flow rate (Qur) was taken from (10)

Results/Conclusions

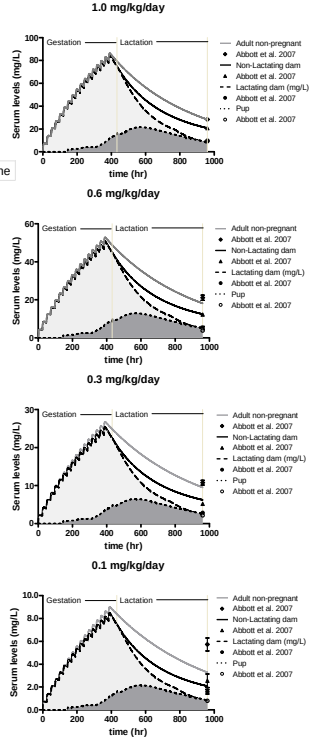
Pharmacokinetic model of gestation and lactation



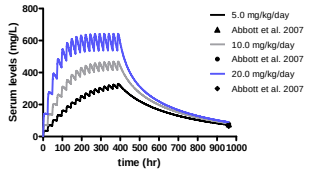
Pharmacokinetic Model for Adult Mice



Simulation of serum levels of PFOA in adult non-pregnant, non-lactating, lactating, and nursing 129S1SvlmJ pups following oral administration of doses ≤ 1 mg/kg/day



Simulation of serum levels of PFOA in adult non-pregnant 129S1SvlmJ mice after oral administration of doses > 1mg/kg/day



Conclusions

• A linear biologically supported model of gestation and lactation reasonably simulated serum levels of PFOA in non-lactating and lactating as well as nursing pups. Serum levels followed the trend: non-pregnant > pregnant(non-lactating) > lactating

• Lactation is predicted to be more important than gestation as a clearance pathway for the dam and correspondingly a major source of exposure for the nursing pups. However, developmentally sensitive periods may render gestation more important toxicologically.

• The incorporation of renal resorption was necessary to simulate the non-linear behavior of serum levels in the adult non-pregnant 129S1SvlmJ mouse, especially at doses > 1 mg/kg at which full-litter resorption occurs in the pregnant mouse.

• These analyses indicate that a linear pharmacokinetic model may be appropriate in the analysis of gestational and lactational exposures to PFOA for doses ≤ 1 mg/kg/day, though this may be dependent on toxicological endpoint and strain.

• These model structures provide an initial template for further explorations of the pharmacokinetics of PFOA in developmental toxicity studies which involve different exposures (in utero, lactational, and post-weaning) but whose current analyses for risk are based solely on the maternal dose.

Acknowledgement

Special thanks to Barbara Abbott, Chris Lau, and Sue Fenton for providing advice and original data in support of these models.

References

(1) Barton, H.A., Lau, I., Lau, C., Hanson, R.G., Lindstrom, A.B., Strynar, M.J., Setzer, R.W. Comparing pharmacokinetic models for perfluorooctanoic acid in mice. Abstract # 1374.
(2) Abbott, B.D., Wolf, C.J., Schmid, J.E., Das, K.P., Zehr, R.D., Helfant, L., Nakayama, S., Lindstrom, A.B., Strynar, M.J., Lau, C. Perfluorooctanoic Acid (PFOA)-induced Developmental Toxicity in the Mouse is Dependent on Expression of Peroxisome Proliferator Activated Receptor-alpha (PPAR). Tox. Sci. 98(2): 571-581 (2007)
(3) O'Flaherty, E.J., Scott, W., Schreiner, C., Bellies, R.P., A physiologically based kinetic model of rat and mouse gestation: disposition of a weak acid. Toxicology and Applied Pharmacology 112, 245-256 (1992)
(4) Lau, C., J. R. Thibodeaux, et al. (2006). Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci **90**(2): 510-8.
(5) Henderson, W. M. and M. A. Smith (2007). Perfluorooctanoic acid and perfluorononanoic acid in fetal and neonatal mice following in utero exposure to 8-2 fluorotelomer alcohol. Toxicol Sci **95**(2): 452-61.
(6) Knight, C. H., E. Maltz, et al. (1986). "Milk yield and composition in mice: effects of litter size and lactation number." Comp Biochem Physiol A **84**(1): 127-33.
(7) Johnson, M. S. and J. R. Speakman (2001). "Limits to sustained energy intake. V. Effect of cold-exposure during lactation in Mus musculus." J Exp Biol **204**(Pt 11): 1967-77.
(8) Russel, F. G. A., A. C. Westerse, et al. (1989). "Physiologically based pharmacokinetic model for the renal clearance of iodopyracet and the interaction with probenecid in the dog." Biopharm Drug Dispos **10**(2): 137-52.
(9) Qi, Z., I. Whitt, et al. (2004). "Serial determination of glomerular filtration rate in conscious mice using FITC-inulin clearance." Am J Physiol Renal Physiol **286**(3): F590-6.
(10) Meneton, P., I. Ichikawa, et al. (2000). "Renal physiology of the mouse." Am J Physiol Renal Physiol **278**(3): F339-51.