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

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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 male (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 129/S1SvlmJ mouse strain (2). Gestation: Gestation was described as a two-compartment (dom + 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, and placenta were taken from (3) and adjusted for the timing of gestation specific for the mouse at 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 gestational day were estimated from (5). The elimination rate constant for the dam and nursing pups were obtained by optimization using nonlinear fitting of 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 as a per pup basis, and fitted to a one- or two-component polynomial function (Graphpad prism). Body weight increases for the lactating dams 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 similarly. BW increases for the pups 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.

Risk Assessment Approach

Matured Exposure

Pharmacokinetics

Sternal Bloodstream

Limited information approach

Pharmacodynamics

Mechanistic of Toxicity

Observed toxicity

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 toxically.

• The incorporation of renal resorption was necessary to simulate the non-linear behavior of serum levels in the adult non-pregnant 129/S1SvlmJ mice, especially at doses > 1 mg/kg at which full-litter resorption occur 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 exploration 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 Albett, Omar Lau, and Sue Fentem for providing advice and original data in support of these models.

References


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