Modeling the Pharmacokinetics of Perfluorooctanoic Acid (PFOA) During Gestation and Lactation in Mice

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Perfluorooctanoic acid (PFOA) is used as a processing aid for the production of commercially valuable fluoropolymers and fluoroelastomers. It has been widely detected in biological organisms including humans whose blood levels range from the low ppb for the general US population to low ppm levels for occupationally exposed workers. PFOA is metabolically stable and exhibits a plasma half-life of 3-5 years in humans. In mice, PFOA induces developmental toxicity in the form of full litter resorption, compromised postnatal survival, delayed development and growth, and altered pubertal maturation. While some postnatally-observed developmental effects have been attributed to gestational exposure, it remains to be elucidated whether these result from a higher internal dose (pharmacokinetics) and/or exposure during a developmentally sensitive period (pharmacodynamics). Furthermore, lactation as an elimination pathway for the dam and an exposure route for nursing pups has not been adequately examined. To address the pharmacokinetics of PFOA during gestation and lactation, a biologically-supported dynamic model was developed. A two compartment system linked via placental blood flow described gestation, while milk production linked the dam to a pup litter compartment during lactation. Mathematical functions described the growth of the dam, conceptus, placental blood flow, and nursing pups. Maternal serum:milk and serum:fetal partition coefficients and milk production were estimated from published literature. Absorption and elimination were described as first order processes. The model reasonably simulated reported serum levels for non-lactating dams at doses $\leq$ 1 mg/kg PFOA, but failed to simulate non-linear behaviors at higher doses. A reduction in the milk elimination rate constant, probably reflecting data gaps in model calibration, was necessary to simulate levels in lactating dams and pups at weaning. Conceptus

levels start low relative to maternal serum but increase rapidly towards the end of gestation as a consequence of the estimated partitioning. These modeling efforts provide an initial template for further explorations of the pharmacokinetics of PFOA relevant to one-generation toxicity studies. (*This work does not reflect official Agency policy*).