MODELING THE PHARMACOKINETICS OF PERFLUOROOCTANOIC ACID 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 estimated blood levels are in the low ppb levels for the general US population. 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 growth and development, 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). 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. Serum:fetal and serum:milk partition coefficients and milk production were estimated from published literature. Absorption and elimination were described as 1st order processes. The model reasonably simulated reported serum levels in non-lactating and lactating dams as well as nursing pups. Lactation is

predicted to be an important 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 mouse, especially at doses > 1mg/kg/day 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 doses of PFOA ≤ 1 mg/kg/day, though this may be dependent on strain and toxicological endpoint. 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).