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

Simulation of serum levels of PFOA in adult non-pregnant, non-lactating, lactating, and nursing 129S1SvlmJ mice after 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 > 1 mg/kg/day

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 for all modeled life stages. All of the serum dosed 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 (QPL). 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 (180-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 coefficient 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 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 as a per pup basis, and fitted to a one-native binding hyperbolic (Gompertzian) type. Body weight (BW) increases for the lactating mother were taken from (7), fitted to a 2nd order polynomial (Gompertzian) type 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 (Gompertzian) type and linked correspondingly to the predicted BW. The maternal plasma partition coefficient was fitted to a value of 0.04 and assumed constant.

Risk Assessment Approach

- Perfluorooctanoic Acid (PFOA) - A fully fluorinated alkyl acid which has been widely used as a surfactant and emulsifier for the production of commercially valuable fluropolymers and Fluorolattomizers.
- 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-life (human plasma half-life estimated at 3-5 years) and clearance can vary dramatically across species, and for some species, across gender.
- Exhibits developmental toxicity in mice in the form of Full-litter resorption, compromised postnatal survival, delayed growth and development, and showed partial euthanasia.
- 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 Management Approach

Pharmacokinetics

- Saturable Dosimetry
- Limited information approach

Pharmacodynamics

- Mechanistic models for Toxicity
- Observed toxicity

Effect of oral route on the mean serum and milk concentration of PFOA in adult non-pregnant (1) and pregnant (2) mice.

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References