

Modeling Single and Repeated Dose Pharmacokinetics of PFOA in Mice

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Perfluorooctanoic acid (PFOA) displays complicated pharmacokinetics in that plasma serum concentration indicates a long half life – 3.8 years in humans (Olsen et al. 2007) – but also rapidly achieves steady-state (Lau et al., 2006). Attempts to address this have included using different pharmacokinetic parameters for different doses (Washburn et al., 2005, Trudel et al., 2008) as well as biologically-based models such as the saturable resorption model of Andersen et al. (2006). We examined plasma concentration time-courses for female CD1 mice after single, oral doses of 1, 10, and 60 mg/kg of PFOA. We found that the pharmacokinetics for the two lower doses are well-described by an empirical, one-compartment model. The predictions for that model are not, however, consistent with the 60 mg/kg data which was instead found to be consistent with a two-compartment model that was in turn inconsistent with the two lower doses. We then examined plasma concentrations observed after 7 and 17 daily doses of 20 mg/kg PFOA from Lau et al. (2006) as well as additional 17-day studies. The 1 and 10 mg/kg one-compartment fit was not consistent with repeated dose concentrations while the 60 mg/kg two-compartment was. We found that some level of consistency between low and high doses could be achieved using the saturable resorption model of Andersen et al. (2006) in which PFOA is cleared from the plasma into a filtrate compartment from which it is either excreted or resorbed into the plasma by a process with a Michaelis-Menten form. A maximum likelihood estimate found a transport maximum of $T_m = 860.9$ (1298.3) mg/L/h and half-maximum concentration of $K_T = 0.0015$ (0.0022) mg/L where the estimated standard errors (in parentheses) indicated large uncertainty. The estimated rate of flow into and out of the filtrate compartment, 0.6830 (1.0131) L/h was too large to be consistent with a biological interpretation of the filtrate. For these model parameters we estimated that a single dose greater than 40 mg/kg, or a daily dose in excess of 5 mg/kg were necessary to observe non-linear pharmacokinetics for PFOA in female CD1 mice. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*