Modeling Single and Repeated Dose Pharmacokinetics of PFOA in Mice

John F. Wambaugh*, Inchio Lou*, Christopher Lau†, Roger G. Hanson†, Andrew B. Lindstrom§, Mark J. Strynar§, R. Dan Zehr†, R. Woodrow Setzer*, and Hugh A. Barton*

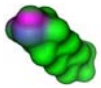
*National Center for Computational Toxicology and
†Reproductive Toxicology Division and §Human Exposure and Atmospheric Science Division, National Exposure Research Laboratory
U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Abstract

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 Tm = 860.9 (1298.3) mg/L/h and half-maximum concentration of KT = 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.

Introduction



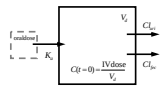
Straight chain PFOA

- We are investigating the pharmacokinetics of PFOA
- Single doses of 1 and 10 mg/kg of PFOA were administered to male and female CD1 mice and concentration time-courses in blood serum, kidney, and liver tissue were observed
- For the female mice only, the serum concentration time-course was also observed for a single dose of 60 mg/kg
- We also examine data from the 20 mg/kg repeated dose study of Lau et al. (2006) that examined serum PFOA concentration 24 hours after 7- and 17-day dosing regimens as well as additional data for a 17-day dosing
- We incrementally analyze subsets of the data, making use of statistical analyses to determine the appropriate model for that subset
- Finally, we analyze all the data, making use of maximum likelihood estimation to determine optimal parameter values and standard errors for the available data

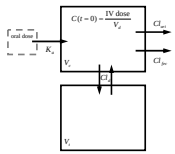
Caprylic acid

Empirical Models for PFOA

One Compartment Model

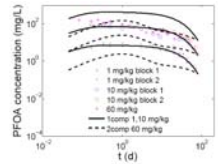


Two Compartment Model

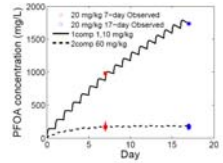


- Simple, empirical models often provide a useful starting point for pharmacokinetic analyses
- For the 1 and 10 mg/kg single dose data (**indicated by . and o**), we find that we can generally estimate parameters for the one compartment model, but not for the two compartment model
- Predictions made using the one compartment model parameters estimated for 1 and 10 mg/kg single doses (**solid line**) do not agree with concentrations observed for single doses of 60 mg/kg (**+**) or repeated dose studies (**day 7 and 17 predictions indicated by squares**)
- For the 60 mg/kg single dose data, the best fit is achieved with the two compartment model
- The 60 mg/kg pharmacokinetics agree with the repeated dose data, but are not consistent with the 1 and 10 mg/kg single dose
- Neither empirical model we examined explains all the observed PFOA pharmacokinetics

Single Dose Predictions

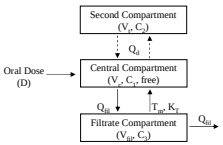


Repeated Dose Predictions

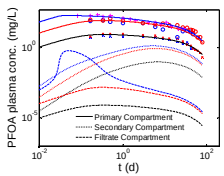


The Saturable Resorption Model

Andersen et al. (2006) Model

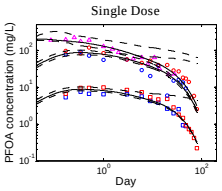


Compartmental Kinetics

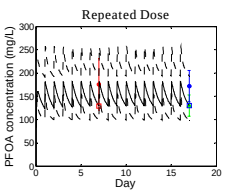


- We then investigated the biologically-motivated "saturable resorption" model of Andersen et al. (2006) and used both the single and repeated dose data to estimate the appropriate pharmacokinetic parameters
- The saturable resorption model allows rapid clearance from the filtrate compartment (**dashed line in compartmental kinetics figure at left**) whenever the resorption back into the primary compartment (**solid**) saturates
- At low dose or in the early period of repeated dose for our data, the PFOA concentration in the filtrate compartment is low and is proportional to dose leading to a low net urine elimination rate
- At higher doses, including the pseudo-steady state for repeated doses the concentration in the filtrate compartment is high and resorption is saturated, which results in a high net urine elimination rate
- In effect, there are two half-lives – a short half-life for higher concentrations that gives way to a slower, roughly 14-day half-life for lower concentrations
- Note the rapid convergence for doses of 10 and 60 mg/kg.

Single Dose

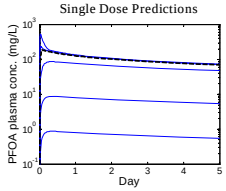


Repeated Dose

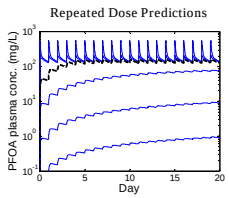


- The model predictions for the optimized parameters (**at left**) are indicated by a solid line, with open squares indicating where model predictions should be compared with observations
- Dashed lines indicate the 95% upper and lower quantiles using the estimated parameter uncertainty.
- Using our model, we investigated what doses of PFOA are predicted to show the two different kinetic behaviors
- Only one phase is predicted at low doses (<40 mg/kg), while two phases occur at the high doses (>40 mg/kg)
- For repeated doses, daily doses of 0.01, 0.1, and 1 mg/kg saturated after about two weeks, while for 5 mg/kg the plasma concentration quickly saturated.
- Within a day of daily doses of 50 and 500 mg/kg, plasma concentration saturated at the same concentration as with 5 mg/kg.
- The estimated parameter uncertainties for Q_{fil}, T_m, and K_T are all quite large, i.e. the estimated standard errors larger than their mean values
- Our optimized value for Q_{fil} does not appear to have a direct physiologic analog

Single Dose Predictions



Repeated Dose Predictions



Conclusion

- The one compartment model is successful in describing the 1 and 10 mg/kg single dose data sets with the estimated values of V_d, k_a and k_e, but fails in predicting the higher, 60 mg/kg single dose and the repeated dose data
- Similarly, although the 60 mg/kg data can be described by a two compartment model, for the optimized parameters that model over-estimates the 1 and 10 mg/kg single dose data
- Neither model predicts the full range of concentrations for single and repeated repeated-dose observations without changing some model parameters drastically from the single dose case
- The saturable resorption model of Andersen et al. (2006) reconciles the lower two doses with the high single dose by allowing the kinetic behavior to change for different exposure levels.

However:

  - The optimized parameters underestimate the Lau et al. (2006) data
  - Estimated parameters for saturable resorption do not seem to be biologically plausible

- Either more repeat dose data or a more elaborate model may be needed to reconcile single and repeat dose PFOA pharmacokinetics.

References

Andersen ME, Clewell HJ, Tan Y, Butenhoff JL and Olsen GW (2006), Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys – Probing the determinants of long plasma half-lives, 227: 156-164, Toxicology

Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB and Strynar MJ (2006), Effects of perfluorooctanoic acid exposure during pregnancy in the mouse, 90(2): 510-518, Toxicological Sciences

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, and Zobel LR (2007), Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers, Environmental Health Perspectives

Trudel, D, Horowitz, L, Wormuth, M, Scheringer, M, Cousins, IT, and Hungerbühler, K (2008), Estimating Consumer Exposure to PFOS and PFOA, 28(2), 251-269, Risk Analysis

Washburn ST, Bingman TS, Braithwaite SK, Buck RC, Buxton LW, Clewell HJ, Haroun LA, Kester JE, Rickard RW, Shipp AM (2005). Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles, 39(11): 3904-3910, Environmental Science and Technology