Enhancing the Modeling of PFOA Pharmacokinetics with Bayesian Analysis

John F. Wambaugh, Hugh A. Barton and R. Woodrow Setzer
National Center for Computational Toxicology, US EPA

The detail sufficient to describe the pharmacokinetics (PK) for perfluorooctanoic acid (PFOA) and the methods necessary to combine information from multiple data sets are both subjects of ongoing investigation. Bayesian analysis provides tools to accommodate these goals. We examined the results of a series of experiments [Kemper, 2003] that observed the concentration of PFOA in male and female adult rats. For some subjects plasma concentration was observed over time, while for others feces and urine were collected. Assuming that the PK parameters for each individual were drawn from the same, biologically-varying population, we jointly analyzed both types of data. This hierarchical approach allowed us to estimate the contributions of uncertainty due to measurement error and actual biological variability.

We performed a Bayesian analysis using Markov Chain Monte Carlo. Since PFOA excretion is known to be sexually dimorphic in rats, we analyzed the male and female data separately. The distributions of integrated plasma concentration (AUC) varied significantly because the clearance is much higher in females (35.6±9.2 mL/kg/h) than in males (0.81±0.24 mL/kg/h).

Starting from a one-compartment PK model with separate clearances to urine and feces, we incrementally expanded the model using Bayesian measures to assess if the expansion was supported by the data. Including excretion data initially decreased certainty in the AUC compared to an analysis using plasma data only. Allowing a third, unspecified clearance improved agreement and increased certainty when all the data was used. However, the PFOA cleared by this third route appeared too large to be experimentally plausible. Adding an additional PK compartment was supported by the data and reduced the unaccounted-for elimination to amounts comparable to the cage wash. Since we have established that the data require more complicated models, PBPK models may provide additional insights.