Assessing Uncertainty in the Toxicology of PFOA

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Any scientific experiment involves uncertainty. For instance, if you flip a coin ten times it might come up heads six times and tails four times. Although you have measured that you get heads 60% of the time, with only ten flips you are not certain of that number. This result is consistent with the coin being fair (probability of heads is 50%), but almost equally consistent with the coin being quite unfair (probability of heads is 70%). For toxicological experiments we wish to quantify the uncertainty of our understanding by assessing both the full range of possible answers and how likely they are to explain available data. We use an approach known as Bayesian statistics to characterize our knowledge about the behavior of a chemical prior to an experiment and make explicit our assumptions about how we think the chemical behaves. When we then analyze the results of an experiment, we determine probability distributions for every variable that tell us not just the most likely value, but also how likely are other, different values. This allows us to completely rule out certain possibilities while still considering other possibilities that, while less likely than the mean, are possible.

We are currently studying data (Kemper, 2003) from 32 adult male rats that have been given different doses of perfluorooctanoic acid (PFOA). Observations were made over time of the concentration of PFOA in either plasma or urine and feces. We use simple pharmacokinetic (PK) models to match the observations by describing the physiology of the rats in terms of one or two compartments that can contain PFOA. We use Markov-Chain Monte Carlo to computationally try millions of different combinations of model parameters for the individual rats, the overall population of rats, and the experimental measurement error. This produces probability distributions that quantify both the uncertainty and variability of the kinetics of PFOA. We have found that using two compartments better describes the observations than a single compartment, without increasing uncertainty. We also have evidence that predicting fecal elimination will require more complicated, physiologically-based models.