Assessing Uncertainty in the Toxicology of PFOA

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BIOLOGICAL MODELS

Overview

Imagine flipping a coin ten times. You might get six heads and four tails. Though you have measured that you get heads 60% of the time, with only ten flips you are not certain of that number.

Your result is consistent with the coin being fair (probability of heads is 50%), but is almost equally consistent with the coin being quite unfair (probability of heads is 70%). Characterizing this **uncertainty** is important for making predictions about future coin tosses.

What if other coins are different? If most are fair but some are trick coins then predicting the outcome of another coin flip will also depend on knowing the coin-to-coin **variability** as well.

We are studying the results of different types of experiments (Kemper, 2003) on male and female adult rats that have been given various doses of **perfluorooctanoic acid** (PFOA).

We use simple **pharmacokinetic 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 **Bayesian statistics** to determine probability distributions for the model parameters and, using a **hierarchical statistical model,** we are also separate experimental uncertainty from inter-individual variability to enhance our predictions.

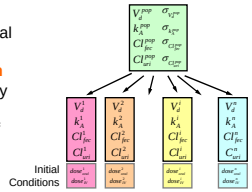
Finally, we are able to compare different models to determine which is most supported by the data.

Analysis Using Bayesian Statistics

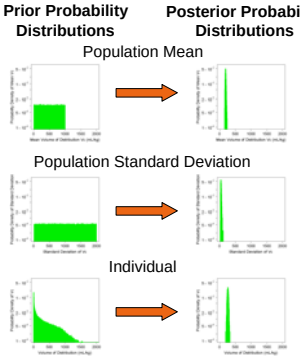
Hierarchical Statistical Model

• We assume that model parameters for each individual are each drawn from the same log-normal **population distribution** characterized by a **mean** and a **standard deviation** of the logarithm of the parameters**.**

• This population approach allows plasma concentration and excretion data to be **used jointly** to estimate population distributions since they provide different types of information about the population parameter distributions.



Bayesian Estimation Using MCMC



• We conduct Bayesian estimation of parameter distributions using Markov Chain Monte Carlo (MCMC) through WinBUGS.

• Each iteration of the **Markov Chain** creates a set of all parameters for a model

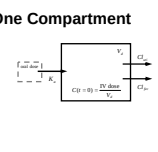
• Sequence of sets in the chain represents the **distribution of parameter values**

• **Convergence** takes between 1,200,000 iterations for single-compartment without excretion data to 4,400,000 iterations using excretion data

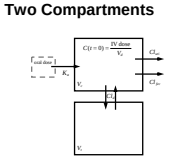
• Single compartment model takes from 6 to 20 hours on a 3-GHz Pentium D computer

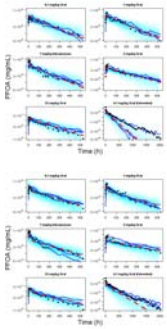
Results

One Compartment



Two Compartments





• We compare predictions using means of estimated population distributions (**red dashed line**) to mean observations of the four individuals (**solid circles)** for each dose.

• The uncertainty in our population distributions is indicated by the **scatter plots**.

• We then simulate the mean of four new individuals (**solid lines**) to indicate the predicted uncertainty from measurement error.

• We make use of the Deviance Information Criterion to compare model appropriateness, which is more than just the goodness of fit.

• We find that for the male rats, an additional compartment is supported even though it introduces two new parameters per animal.

Conclusion

• We estimate pharmacokinetic parameters for PFOA using multiple types of data sets

• For every parameter, we separately estimate measurement uncertainty and population variability.

• We find some justification for a two-compartment model approach for the pharmacokinetics of PFOA

References

Kemper, R. A., "Perfluorooctanoic acid: toxicokinetics in the rat," DuPont Haskell Laboratories, Laboratory Project ID: DuPont-7473. USEPA Administrative Record AR-226.1499 (2003)

Bayesian Data Analysis, Gelman, A., Carlin, J. B., Stern, H. S., and Rubin, D. B., Second Edition, New York, Chapman and Hall (2004).