**The use of a simple pharmacokinetic model to evaluate the effect of ongoing blood loss on human serum concentrations of perfluorinated acids**

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**Introduction**

Perfluorinated alkyl acids (PFAAs) have been detected in serum at low concentrations in background populations. Higher concentrations have been observed in adult males compared to females, with a possible explanation that menstruation offers females an additional elimination route. In this study, we examined the significance of blood loss as an elimination route of PFAAs using a simple pharmacokinetic model. Pooled serum samples were collected from individuals in Australia undergoing a medical procedure involving ongoing blood withdrawal called venesection. These results have been previously reported (1). Briefly, 151 samples were collected, and from these, 33 pooled samples (6 samples per pool; 23 pools representing males and 10 pools representing females) were created. These pools were created by considering the number of venesection treatments (< 10, >10), and "replenishment" time from last venesection to when final blood measurements were made in 2009 (< 365, > 365 days). Concentrations from male venesection patients were approximately 40% lower than males in the general population for perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). A simple pharmacokinetic model was used to test the hypothesis that blood loss could explain why males undergoing venesections had lower concentrations compared to males in the general population, and why adult males in the general population have higher concentrations than females.

**Model Description**

The PK model is a simple 1-compartment, first order model previously calibrated and used to study accumulation of PFOA and PFOS in the general population in Australia (2). At steady state, the simple 1-compartment model can be solved for concentration as:

$$C(ss) = [ D / (kP * Vd) ] \quad (1)$$

where C(ss) is the steady state concentration of a given PFAA in the serum (ng $mL^{-1}$), D is the constant daily absorbed intake dose (ng $kg^{-1}$ $day^{-1}$), kP is if the first order elimination rate ($day^{-1}$), and Vd is the volume of distribution (mL $kg^{-1}$). Values of 170 and 230 mL $kg^{-1}$ were assigned for the Vd's of PFOA and PFOS respectively, and kP's of 0.0008 $day^{-1}$ for PFOA and 0.0003 $day^{-1}$ for PFOS were used. These parameters were calibrated using real world data (2). Then, given the Australian male population blood concentrations of 5.9 ng/mL for PFOA and 16.6 ng/mL for PFOS, we rearranged Equation (1) to estimate general male population PFOA and PFOS intakes of 0.80 and 1.15 ng/kg-day, respectively (2).

The model was run in an iterative, simulation mode on an Excel© spreadsheet, beginning in January of 2004 (when venesection data was first available) with initial serum concentrations at background levels. The spreadsheet maintained mass balances of PFOA and PFOS, and concentrations, when needed, were equal to the mass divided by the volume of distribution, Vd. The time interval was 1 month. The only intake was a background intake and general elimination from the reservoir was modeled as a first order process. Each venesection involved the withdrawal of 450 mL whole blood, or 225 mL of serum. This same volume was withdrawn for each venesection event, regardless of the individual's gender, weight, age, or other factors. The amount of PFAA mass (ng) removed during each event is calculated as 225 mL * concentration at the end of previous time step of the model (ng $mL^{-1}$). Simulations of PFOA and PFOS were run for each of the 23 composite samples representing male venesections. For each composite, precise times of venesection were input to the model, and the blood reservoir was allowed to replenish until the sampling date in 2009. For evaluating menstruation, a simulation started at the background body burden found in males at 5.9 ng/mL PFOA, with removals of PFOA by menstruation occurring once per month until a new steady state was reached. Assuming a 35 mL blood loss during menstruation, 50% of

which is serum, the monthly loss is then modeled as 17.5 mL * serum concentration at the beginning of the previous month (ng/mL).

**Results and Discussion**

Modeled PFOA serum concentrations over time are also shown for a single composite sample in Figure 1 showing the effect of venesection and replenishment time on the serum concentrations. As seen in Figure 1, the discrete venesection events lead to immediate decline in the concentrations. The interval time between venesections, and more so the replenishment time after the last venesection, shows how the model seeks to return the body burden to the initial steady state. The data used for this figure was from a single composite of male patients, characterized according to our pooling strategy as 'all ages', with ⩽10 venesections and >365 days replenishment time.

The results for each of the 23 simulations of males for PFOA and PFOS are shown in Figures 2 and 3, respectively. The average simulated concentration of PFOA was 3.7 ng/mL, a 37% decline from the initial assumed concentration of 5.9 ng $mL^{-1}$. The observed average concentration in the venesection patients was 3.4 ng $mL^{-1}$, 42% less than background. Hence for PFOA the model is in very good agreement with the mean of the measured data. For PFOS, the model predicts a concentration drop from 16.6 ng $mL^{-1}$ serum to 7.9 ng mL-1 in the venesection group, a 52% decline, where the mean measured concentration was substantially higher at 11.2 ng $mL^{-1}$, or only 33% lower than background. Although the model agreement was poorer for PFOS, overall, the modeling results support the hypothesis that the lower concentrations seen in venesection patients can be explained through the loss of PFAAs via loss of blood during venesection.

The simulation of menstruation is shown in Figure 4. The body burden begins at 5.9 ng $mL^{-1}$, the presumption of what it might be without the menstrual loss. It is seen that steady state is regained after about 8 years at a new lower body burden of 4.6 ng $mL^{-1}$, a 22% reduction. This is in remarkably good agreement with the observed mean body burden in women of 4.5 ng/mL, 24% lower than in adult males. It provides supportive evidence for the finding that menstrual losses could explain the difference in male and female body burdens.

## References


1. Thompson J, Toms L-ML, Eaglesham G, Hobson P, Mueller, JF. (2010a); *Organohalogen Comp* 72: 826-29.
2. Thompson J, Lorber M, Toms L-ML, Kato K, Calafat AM, Mueller JF (2010b); *Env Int* 36(4): 390-397.


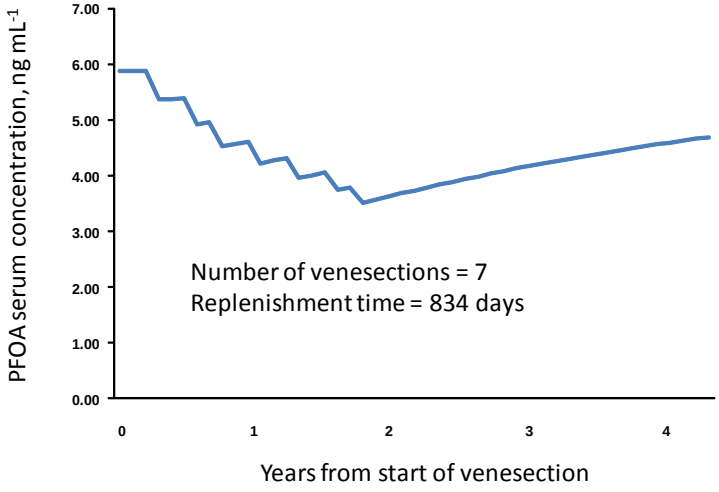


**Figure 1 Modeled serum PFOA concentration profile with time for a single composite sample**

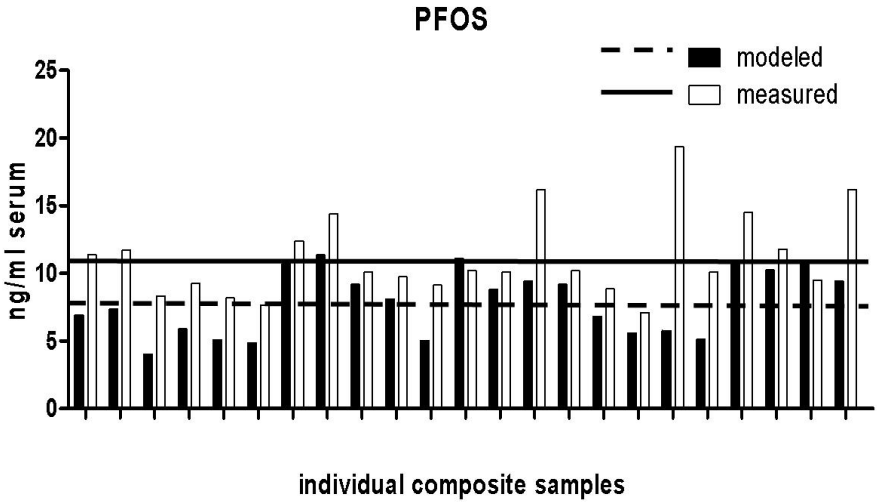


**Figure 2 Measured and modeled concentrations of PFOS (ng/mL in serum) across all 23 composite samples of male venesection patients, with horizontal lines representing average values for both**

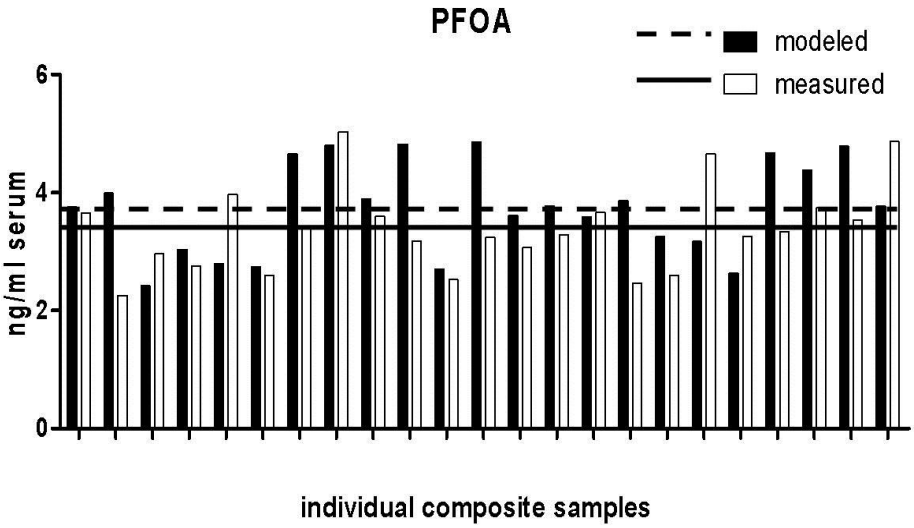


**Figure 3 Measured and modeled concentrations of PFOA (ng/mL in serum) across all 23 composite samples of male venesection patients**.

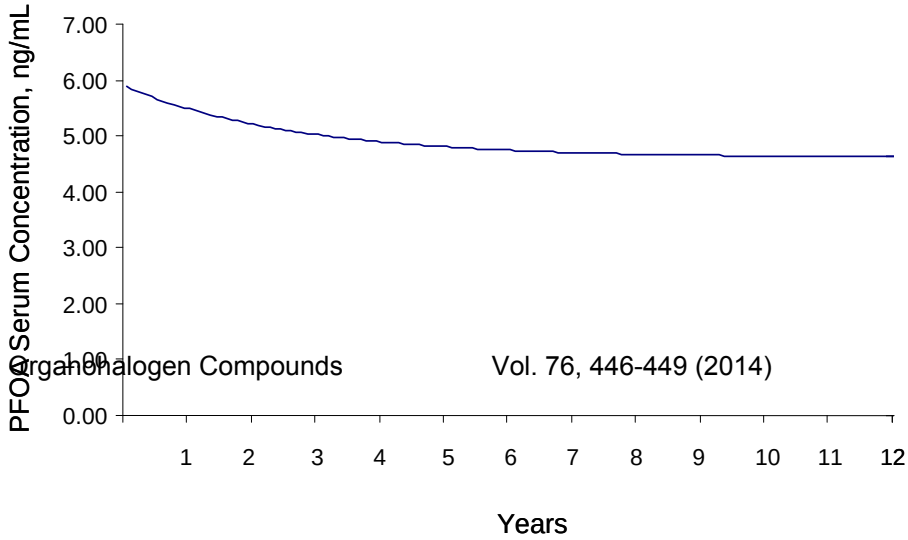

**Figure 4 Modeled reductions in serum PFOA concentration due to menstruation.**