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The effect of ongoing blood loss on human serum concentrations of perfluorinated acids

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HIGHLIGHTS

- We investigate if blood loss reduces body burdens of perfluorinated acids, PFAAs.
- PFAAs were lower in males requiring regular blood withdrawals for a medical condition.
- Pharmacokinetic (PK) modeling was able to duplicate this finding.
- PK modeling also showed that menstruation would also reduce PFAAs in women.

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ABSTRACT

Perfluorinated alkyl acids (PFAAs) have been detected in serum at low concentrations in background populations. Higher concentrations haven 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. Pooled serum samples were collected from individuals undergoing a medical procedure involving ongoing blood withdrawal called venesection. Concentrations from male venesection patients were approximately 40% lower than males in the general population for perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). A simple pharmacokinetic model was used to test the hypothesis that blood loss could explain why adult males have higher concentrations of PFAAs than females, and why males undergoing venesections had lower concentrations compared to males in the general population. The model application generally supported these hypotheses showing that venesection might reduce blood serum concentrations by 37% (PFOA) and 53% (PFOS) compared to the observed difference of 44% and 37%. Menstruation was modeled to show a 22% reduction in PFOA serum concentrations compared to a 24% difference in concentrations between males and females in the background population. Uncertainties in the modeling and the data are identified and discussed.

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1. Introduction

Perfluorinated alkyl carboxylic and sulfonic acids are two groups of perfluorinated alkyl acids (PFAAs) compounds classes of man-made compounds in use since the 1950's in various industrial and consumer applications. These include use in oil and water resistant surface coatings, in aqueous film fire-fighting foams (AFFFs), and in the process of fluoropolymer manufacturing (Prevedouros et al., 2006; OECD, 2002). Due to environmental

Abbreviations: AFFF, aqueous film fire-fighting foams; C, concentration of a PFAA in serum; D, daily intake dose; kP, first order elimination rate; NHANES, National Health and Nutritional Evaluation Survey; PFAA, perfluorinated alkyl acid; PFBA, perfluorobutanoic acid; PFBS, perfluorobutane sulfonate; PFDoDA, perfluorododecanoic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFPeA, perfluoropentanoic acid; PFUnDA, perfluoroundecanoic acid; PK, pharmacokinetic; Vd, volume of distribution.

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concerns regarding their persistence and potential adverse health effects, in recent years their production and use has been limited and discouraged in many areas (NICNAS, 2007, 2008; Wang et al., 2009). The eight carbon anion of the sulfonic acid, perfluorooctane sulfonate, PFOS, has been added to the Stockholm convention which aims to reduce persistent organic pollutants in the environment (Stockholm Convention, 2010). However, PFAAs are still used in the semi-conductor and metal plating industries, and other PFAA containing products, such as specialty AFFFs, treated carpets and textiles, are likely present in stockpiles and inventories until their use or disposal and replacement. PFAAs have been measured in wildlife and human populations from around the globe (Houde et al., 2006). The route of human exposure to these compounds is not entirely elucidated, but a considerable portion appears to come from diet (Fromme et al., 2009; Lorber and Egeghy, 2011; Egeghy and Lorber, 2011).

Multiple studies have found significant differences between adult male and female serum concentrations of both PFOS and/or PFOA (Olsen et al., 2005; Calafat et al., 2007; Toms et al., 2009), with males having higher concentrations than females. For instance in data from South East Queensland, Australia, where the current study was conducted, samples pooled by age (30 individuals per pool) showed higher concentrations of PFOS in all male pools over 16 years by 2.5–5.6 ng mL^{-1}. For PFOA the differences were smaller, 0.9–2.4 ng mL^{-1} (Toms et al., 2009). In data from the 2003/2004 National Health and Nutritional Evaluation Survey (NHANES) in the US, the male geometric mean PFOS concentration was 23.3 ng mL^{-1}, compared with 18.4 ng mL^{-1} in females. For PFOA the same comparison was 4.5 ng mL^{-1} and 3.5 ng mL^{-1} (results for individuals > 12 years; Calafat et al., 2007). Toms et al. (2014) looked at trends in PFAA serum concentrations of Australians between 2002 and 2011. They found that males had higher concentrations of PFOS, PFOA, PFNA, and PFHxS from about age 15 until age 60, and after age 60, males and females had similar concentrations. This is not consistent in every study, and some have found no significant differences (Kubwabo et al., 2004). However, when observed, the differences have typically been between males and females from the approximate ages of 13–50 years, with little gender differences outside this range (Harada et al., 2005; Ingelido et al., 2010; Toms et al., 2009, 2014). Given this age dependence, it has been suggested that menstruation is an additional route of elimination available to reproductively mature females (Harada et al., 2005), as it is for other xenobiotics (Silvaggio and Mattison, 1994; Soldin and Mattison, 2009). There are certainly other factors affecting the observed patterns in body burden, such as physiological differences, differences in exposure pathways, and the history of child birth in the females studied. Despite this, menstruation and blood loss remains an obvious point of contrast and an intuitive candidate for an additional elimination mechanism.

With this as background, we sought to investigate the effect of blood loss on serum PFAA concentrations in humans. This was done via chemical analysis of serum, combined with the use of a simple pharmacokinetic (PK) model. The serum data originated from persons undergoing regular venesection, also termed phlebotomy. Venesection is a medical practice whereby a quantity of blood is withdrawn from an individual in order to relieve symptoms of disorders such as haemochromatosis. We observed that both males and females showed lower PFAA concentrations than their counterparts in the general population (details below). Then, through application of the PK model, we examine whether or not the observed lower male PFAA body burdens can be explained by loss of PFAAs via loss of blood during these procedures. We then additionally use the model to examine whether difference in males and females in the general population can be explained by menstrual loss of blood.

2. Materials methods

2.1. Sample collection/pooling

Archived de-identified serum samples stored at −20 °C were obtained through Sullivan-Nicolaides Pathology from patients undergoing venesection treatment, for the conditions of either haemochromatosis (99% of donors) or polycythaemia (1% of donors). All samples were originally collected from individuals in the course of unrelated blood work (e.g. health checkups) in 2009. Patient records were available providing only age, date of sample collection (again all collected in 2009), number and dates of venesections since their treatment began in 2004, and the condition requiring venesection. In total, archived serum from 151 individuals was obtained. Composite samples were then created, with each comprised of material from six individual samples, pooled according to: gender, age (three strata: '>60 years', '60 years or less', 'all ages'), number of venesections since 2004 (two strata: '>10', '10 or less') and time since last venesection before 2009 sampling (two strata: '>365 d', '365 d or less') termed hereafter 'replenishment time'. We established these strata based on an examination of the data, believing they would reasonably explore the effects of the total volume of serum lost and the replenishment of the body with PFAAs through background intakes. Further, the pooling of samples was an essential component of the study's ethical requirements. The pooling resulted in a total of 33 composite samples, 23 male and 10 female. We focus here on 15 of the male and 7 of the female composites. All of these 22 were in the stratified age-specific pools: either the '>60 years' or the '60 years or less' groups, depending on age. There were six independent serum samples contributing to each composite, and so these 22 composites represented 132 individuals. The other 11 pools were termed, 'all ages' pools. There were 8 male and 3 female 'all ages' pools. These 'all ages' pools were comprised of serum samples, some of which had also been used in the age-specific pools. Since there was some duplication (repeat usage of individual serum samples) in these 'all ages' pools, including them in statistical analyses would be invalid. For this reason, we do not provide and analyze the 'all ages' results here; a summary of results from them are provided in Supplementary Material.

An age bias is seen in the individuals sampled; specifically that there were a larger number of older individuals in the full cohort of 151 original individuals as compared to younger individuals. This is because the conditions requiring venesection tend to not manifest negative effects until later in life. In the final pooled samples, 9 of the 15 age-specific pools for males and 5 of the 7 age-specific pools for females were for the age range >60 years. Regarding the other pool characteristics, 10 pools were characterized as having greater than 10 venesections, leaving 12 for 10 or less venesections, and 10 pools were greater than 365 d since last venesection and sampling leaving 12 with 365 d or less.

To provide a general population 'control' group for comparison, data were compared with results from pooled serum samples collected from individuals living in South East Queensland (Toms et al., 2014). To ensure a valid comparison of the two data sets, four of these pools were retrieved and analyzed in duplicate at our laboratory along with the new serum pools. Results of this validation are provided in Supplementary Material. Ethics approval for this study was granted by The University of Queensland Medical Research Ethics Committee.

2.2. Extraction and analysis

A solution of isotope labeled PFAAs (1 ng) was added to 1 mL of each pool, consisting of $^{13}C_4$-perfluorobutanoic acid (^{13}C-PFBA),