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Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid

Jack Thompson [a,*], Matthew Lorber [b], Leisa-Maree L. Toms [a], Kayoko Kato [c], Antonia M. Calafat [c], Jochen F. Mueller [a]

[a] The University of Queensland, National Research Centre for Environmental Toxicology, 39 Kessels Road, Coopers Plains, QLD, 4108, Australia
[b] Office of Research and Development, United States Environmental Protection Agency, 1200 Pennsylvania Ave, Washington, District of Columbia 20460, USA
[c] Centers for Disease Control and Prevention, Atlanta, GA, 30341-3724, USA

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ABSTRACT

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) have been used for a variety of applications including fluoropolymer processing, fire-fighting foams and surface treatments since the 1950s. Both PFOS and PFOA are polyfluoroalkyl chemicals (PFCs), man-made compounds that are persistent in the environment and humans; some PFCs have shown adverse effects in laboratory animals. Here we describe the application of a simple one compartment pharmacokinetic model to estimate total intakes of PFOA and PFOS for the general population of urban areas on the east coast of Australia. Key parameters for this model include the elimination rate constants and the volume of distribution within the body. A volume of distribution was calibrated for PFOA to a value of 170 ml/kg bw using data from two communities in the United States where the residents' serum concentrations could be assumed to result primarily from a known and characterized source, drinking water contaminated with PFOA by a single fluoropolymer manufacturing facility. For PFOS, a value of 230 ml/kg bw was used, based on adjustment of the PFOA value. Applying measured Australian serum data to the model gave mean ± standard deviation intake estimates of PFOA of 1.6 ± 0.3 ng/kg bw/day for males and females >12 years of age combined based on samples collected in 2002–2003 and 1.3 ± 0.2 ng/kg bw/day based on samples collected in 2006–2007. Mean intakes of PFOS were 2.7 ± 0.5 ng/kg bw/day for males and females >12 years of age combined based on samples collected in 2002–2003, and 2.4 ± 0.5 ng/kg bw/day for the 2006–2007 samples. ANOVA analysis was run for PFOA intake and demonstrated significant differences by age group ($p = 0.03$), sex ($p = 0.001$) and date of collection ($p < 0.001$). Estimated intake rates were highest in those aged >60 years, higher in males compared to females, and higher in 2002–2003 compared to 2006–2007. The same results were seen for PFOS intake with significant differences by age group ($p < 0.001$), sex ($p = 0.001$) and date of collection ($p = 0.016$).

1. Introduction

Polyfluoroalkyl chemicals (PFCs) such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) have been used commercially since the 1950s for a variety of applications including fluoropolymer processing, fire-fighting foams, and paper and textile surface treatments (Paul et al., 2009; Prevedouros et al., 2006). Both PFOA and PFOS have received attention in recent years due to persistence in both the environment and humans (Giesy and Kannan, 2002). Unlike legacy lipophilic persistent pollutants such as polychlorinated biphenyls and dichlorodiphenyltrichloroethane, PFCs bind to blood proteins such as albumin (Han et al., 2003). In animal systems PFOA and PFOS have been shown to be peroxisome proliferators, hepatotoxic and potentially carcinogenic (Kennedy et al., 2004; OECD, 2002). Epidemiologically no definitive correlations have yet been observed between PFC serum concentrations in human populations and adverse health effects or illness (Alexander and Olsen, 2007; Emmett et al., 2006a). However some correlations have been reported with regards to human reproductive health (Olsen et al., 2009), and between PFOA/PFOS and cholesterol levels, which have potentially serious implications regarding risk from heart disease (Steenland et al., 2009). The persistence of PFCs in the environment and slow elimination rates in humans means they are likely to accumulate in people. This is supported by the consistent detection of both PFOA and PFOS in the blood of the general population of various countries (e.g. Calafat et al., 2007; Yeung et al., 2008).

In response to environmental concerns, production of PFOS was ceased by 3 M, its major manufacturer, in 2002 (OECD, 2002); in Australia usage has ceased in all areas except those where alternatives

* Corresponding author. Tel.: +61 7 3274 9060; fax: +61 7 3274 9003.
E-mail address: jthompson@entox.uq.edu.au (J. Thompson).

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are not available (NICNAS, 2007a). In 2009, PFOS was added to the Stockholm Convention against persistent organic pollutants but continues to be manufactured in countries such as China (Wang et al., 2009). The use and import of PFOA in Australia has been discouraged by the relevant authority (NICNAS, 2007b). In the United States, the 2010/15 PFOA stewardship program implemented by the United States Environmental Protection Agency (USEPA) in conjunction with eight major manufacturers aims to reduce PFOA emissions by 95% by 2010 and the cessation of all production is aimed at for 2015 (US EPA, 2009). Despite the increased regulation of these compounds, exposure to the general public may be expected to continue for some time.

In this work we describe the application of a simple 1st order one compartment pharmacokinetic (PK) model to previously reported PFOA and PFOS concentrations from pooled serum samples collected from the general population in urban centers on the east coast of Australia. Models of the type used here have previously been used to estimate intakes for various PFCs using both forward (i.e. from concentrations in exposure media such as food (e.g.Fromme et al., 2007)) and backward (from concentrations in the body (Trudel et al. 2008)) approaches. Although a range of PFCs are being found in humans and the environment, the model is applied here to PFOA and PFOS only, due to the predominance of these compounds in serum.

2. Methods

2.1. Modeling

A simple, single compartment, 1st-order pharmacokinetic (PK) model which predicts PFOA and PFOS concentrations in blood serum as a function of dose, elimination rate, and volume of distribution, is used in this study. This model is given as:

$$d(CP)/dt = (DP(t))/Vd - kP \times CP(t) \quad (1)$$

where CP is the serum concentration (ng/ml) of the target chemical (PFOS or PFOA), DP is the daily absorbed dose (ng/kg bw/day), Vd is the volume of distribution (ml/kg bw), and kP is the first-order elimination rate in the body (day^{-1}). Assuming steady state conditions exist, one can easily solve for blood serum concentration and intake dose as:

$$CP = DP/(kP \times Vd) \quad (2a)$$

and

$$DP = CP \times kP \times Vd \quad (2b)$$

Or rearranged to calculate the volume of distribution (Vd)

$$Vd = DP/(CP \times kP) \quad (2c)$$

2.1.1. Calibration of the volume of distribution (Vd) parameter

The volume of distribution is defined as the total amount of a substance in the body divided by its concentration in the blood or serum (Vd [ml/kg bw] = mass in body [ng/kg bw]/concentration in blood or serum [ng/ml]) (Birkett, 1988). While Vd likely has a physiological underpinning specific to the contaminant and the animal species in which it is applied, it is best thought of as a modeling parameter which needs to be carefully assigned. Previous PFC modeling has relied upon Vd values obtained through animal dosing studies (e.g. Harada et al., 2003; Washburn et al., 2005), such as those estimated by Andersen et al. (2006), Griffith and Long (1980), or Seacat et al. (2002). In this work a value was calibrated from human serum and exposure data. Specifically, we used data from two communities where drinking water supplies had been contaminated with PFOA from a single fluoropolymer manufacturing facility. The higher than background serum PFOA concentrations of residents in these communities have been related to exposure to the contaminated drinking water, and well characterized serum and water concentration data were available for both communities. The full details of this calibration exercise are provided in the supplementary material. Briefly, average water concentrations were multiplied by an assumed daily consumption rate (1.4 L/day (EPA, 1997)) and an assumed gastrointestinal absorption fraction of 91% to give a daily dose (DP) to be used in Eq. (2c). As discussed below, a high GI absorption was justified based on the high absorption rates seen in animals (Hundley et al., 2006; OECD, 2002). 91% was chosen specifically following the example of Trudel et al. (2008) who used this value in their 'high' exposure modeling scenario based on the 95th percentile of the Hundley *et al.* results. The average serum PFOA concentrations were used as the CP term, and with this information, similar values for Vd were obtained for both communities (173 ml/kg bw and 165 ml/kg bw). The average value of 170 ml/kg bw was used as the Vd for application to the Australian serum PFOA data.

2.1.2. Final model inputs: application to the Australian data

A list of the parameters used in the model applied to the Australian serum data are given in Table 1 and described in detail below.

1) Australian pooled serum PFOA and PFOS concentration data (CP)
   Concentrations of PFOA and PFOS have been determined in pooled serum samples collected in 2002–2003 and 2006–2007 from Australian residents. Details of the population stratification (sex, age (<15, 16–30, 31–45, 46–60 and >60 years), and region), analyses and results have been published previously (Karrman et al., 2006; Toms et al., 2009). The 2002–2003 pools consisted of 1 ml of serum samples from 100 individual donors, the 2006–2007 pools contained 1 ml serum samples from 30 individual donors.
   For the purposes of modeling, a mean age for each pool was calculated from the average individual donor ages contributing to the pool. Only data for ages >12 years were used because the application of the pharmacokinetic model is considered only valid for steady state conditions as could be expected from long-term background exposures. The only exception is in the 2002–2003 samples where the males <16 years had a mean age of 11 years but were still included in intake calculations. The mean age along with age specific typical body weights (Australian Bureau of Statistics, 2008) were used in the calculation of intakes. Descriptive statistical analysis was used to estimate average intake doses, standard deviations and ranges. ANOVA analysis was undertaken incorporating age group, gender and collection period. The conventional 5% cut-off was used to report results as statistically significant. Statistical analysis was carried out using SPSS 17.0. (SPSS Inc./Chicago IL, US).
2) Elimination rate constants (kP)
   The elimination rate constants ($kP = \ln 2/t_{1/2}$) were assigned values of 0.0008 day^{-1} (PFOA) and 0.0003 day^{-1} (PFOS). The elimination rate for PFOA was based on a serum half life of 2.3 years, taken from a recent study examining the declining serum concentrations in the same US communities as used for the Vd calibration exercise, after steps were taken to reduce water supply contamination (Bartell et al., 2010). The PFOS elimination rate was based on the results of an occupational cohort study suggesting serum half lives of 5.4–5.9 years (Olsen et al., 2007).
3) Volume of distribution (Vd)
   As described briefly above and in detail in the supplementary material, a Vd value of 170 ml/kg bw was calibrated for PFOA based on available human specific data. A study by Andersen et al. (2006) which calculated values for both PFOS and PFOA, suggested a Vd for PFOS 20–50% greater than that for PFOA, depending on route of exposure (i.e. oral or intravenous). Using the average of