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Changes in serum levels of perfluoroalkyl substances during a 10-year follow-up period in a large population-based cohort

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ABSTRACT

Poly- and perfluoroalkyl substances (PFASs) are a group of man-made fluorinated chemicals which have, at background levels, been associated with negative health effects in humans. Thus far, most human biomonitoring studies have evaluated the general change in PFAS concentration over time by continuously testing various individuals. This is one of the few studies to report the longitudinal trend of a range of PFAS concentrations in humans. In addition, this is the first known longitudinal study to include a large background level exposed cohort of both men and women with the same age and location who were repeatedly sampled from 2001 to 2014.

The longitudinal change in concentration of eight PFASs detected in serum collected from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort were determined and compared to results from general population studies. The sex-dependent changes in PFAS concentrations over time were also assessed. Serum was sampled from the same individuals at ages 70 (collection period 2001–2004), 75 (2006–2009) and 80 (2011–2014,). Eight (C_{6-11}) of fourteen (C_{4-13}) analyzed PFASs were usually detected in over 75% of individuals and assessed using a random effects (mixed) model.

In the 579 individuals attending all three examinations, PFOSA and PFOS concentrations significantly decreased, while the remaining six PFASs significantly increased between ages 70 and 75. However, between ages 75 and 80 all PFAS concentrations significantly decreased. Overall from age 70 to 80, concentrations of PFHxS, PFUnDA, PFNA, and PFDA showed a significant increase (7% to 34%), whereas concentrations of PFOSA, PFHpA, PFOS, and PFOA (−75% to −27%) significantly decreased. Over time PFHxS concentrations increased more among women, while PFHpA concentrations showed a greater decrease among men.

From age 70 to age 80, spanning from 2001-2004 to 2011–2014, the PIVUS cohort showed decreases in circulating levels of some PFASs phased out of production with the exception of PFHxS and $C_{>8}$ PFASs. Contrary to other studies, PFHxS concentrations showed the greatest overall increase, which is likely attributed to a local drinking water contamination incident.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are anthropogenic compounds that have become ubiquitous in our environment due to heavy use in industrial processes since the late 1940s and 50s (D'Eon and Mabury, 2007). Perfluoroalkyl acids (PFAAs), a class of PFASs, are characterized by the replacement of all hydrogen atoms with fluorine atoms in the alkyl chain attached to the acid moiety, making them suitable surfactants for a variety of applications, including aqueous firefighting foams (AFFFs), water, oil and stain repellents, metal plating, and hydraulic fluids in aviation (Buck et al., 2011; Lindstrom et al., 2011). They are also break down products of other precursor compounds, like perfluorooctane sulfonamide (PFOSA) used in similar applications (D'Eon and Mabury, 2007; Lindstrom et al., 2011). They are inherently environmentally persistent and can have long half-lives in humans (2–29 years for different compounds) (Zhang et al., 2013). However, thus far reported PFAS half-lives in humans widely vary due to limited testing (Olsen et al., 2007; Zhang et al., 2013).

Humans are exposed to long-chain PFASs like perfluorocarboxylic acids (PFCAs, $C_nF_{2n+1}COOH$, $n \geq 7$) and perfluorosulfonic acids (PFSAs, $C_nF_{2n+1}SO_3H$, $n \geq 6$) (Buck et al., 2011) primarily through dietary intake of fish, meat and dairy products, whereas drinking water is a major source of exposure to short-chain PFASs (Rahman et al., 2014; Sjogren et al., 2016). Today, perfluorooctane sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS), two PFSAs, and perfluorooctanoic acid (PFOA)

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and perfluorononanoic acid (PFNA), two PFCAs, are the four PFASs found at the highest concentration in humans in most areas of Western countries, while East Asian countries may show higher levels of long chain PFCAs, in particular PFUnDA (Harada et al., 2011; Lau et al., 2007; Salihovic et al., 2015). PFASs have also recently been linked to a number of negative health effects in humans. Large human epidemiological studies, like the C8 health study, show association between a population exposed to drinking water contaminated with PFASs (most notably PFOS and PFOA) and elevated cholesterol, delayed puberty in girls, ulcerative colitis, early menopause, thyroid disease in women, and osteoarthritis (Frisbee et al., 2009; Innes et al., 2011; Knox et al., 2011; Steenland et al., 2013; Steenland et al., 2009). The U.S. National Health and Nutrition Examination Survey (NHANES), a population with background exposure to PFASs, also observed a positive association between PFOS, PFOA, and PFNA concentrations and total and non-high density cholesterol (Nelson et al., 2010). Also diabetes prevalence has been linked to PFNA concentrations in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort (Lind et al., 2013).

Due to increasing concern regarding the toxicological effects of PFASs, several measures were taken to lower human exposure, including the addition of PFOS and PFOS precursor chemicals to the Stockholm Convention in 2009 (UNEP, 2010). However, complete removal of PFASs is not yet feasible because no sufficient alternatives have been found and PFOS and related substances are still manufactured in other countries including India, Poland, China and Russia (Wang et al., 2014; Zhang et al., 2012). In an effort to lower the bioaccumulation of PFASs while still benefiting from their valuable chemistry, long-chain PFAAs were replaced by a number of short-chain PFCAs and PFSAs that are still presently used world-wide (Blum et al., 2015). However, as stated in "The Madrid Statement on Poly- and Perfluorinated Substances", even though short-chain replacement PFASs have faster elimination rates, they are practically indestructible in water and plants and difficult to remove from the water phase, thus providing humans with a constant source of exposure (Blum et al., 2015).

Longitudinal investigations provide an individual-based assessment of the change in concentrations of analytes in a population over time, however few studies have reported recent longitudinal trends of PFASs in humans (Gribble et al., 2015; Nøst et al., 2014). General population trend studies have been the more commonly used practice for monitoring and assessing the temporal changes in PFAS concentrations in humans in various locations around the world, including Australia (Toms et al., 2014), Germany (Schröter-Kermani et al., 2013; Yeung et al., 2013a, 2013b), the U.S. (Kato et al., 2011; Olsen et al., 2012), Sweden (Sundström et al., 2011), Norway (Haug et al., 2009), Denmark (Bjerregaard-Olesen et al., 2016), Japan, Korea and Vietnam (Harada et al., 2011; Okada et al., 2013). These studies often do not account for the variation associated with sampling a continuously changing test group, which can introduce unwanted error. Thus a cohort-based longitudinal investigation involving the same male and female participants would provide more unique and elucidative results as to how a subpopulation may exhibit different trends in PFAS exposure compared to other general populations.

The present study mainly describes the longitudinal trends of eight (C_{6-11}) PFAS concentrations detected in serum collected from the PIVUS cohort from the age of 70 to the age of 80, where the age and location were the same in all individuals, and we also evaluated if sex-specific changes over time in levels of PFASs occurred.

2. Materials and methods

2.1. Sample collection

Serum samples from 1016 70 year-old participants (50.2% women) from Uppsala, Sweden were collected between April 2001 and June 2004 for an epidemiological study known as The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (Lind et al., 2006). The subjects were invited from the general population register in the city of Uppsala by mail and approximately half of the invited subjects participated. An analysis of the disease profile of the attending vs non-attending subjects has been performed and given in detail in (Lind et al., 2006). In short, the attending population was somewhat healthier than the non-attending subjects, however the difference was not great.

The same remaining participants were resampled when they turned 75 years old ($n = 822$; sampled from 2006 to 2009) and 80 years old ($n = 603$; sampled from 2011 to 2014). Of these, 579 participant's serum samples were present in all three collections, and only data from those subjects were included in further analyses (Fig. S1). All serum samples were collected in the morning after an over-night fast and the samples were stored at ≤20 °C until analysis. The study was approved by the Ethics Committee of the University of Uppsala and the participants gave a written informed consent.

2.2. Sample preparation and instrumental analysis

The sample preparation (Table S1) and instrumental analysis (Table S2) methods used in this study were previously developed and validated in terms of recovery, accuracy and precision (Salihovic et al., 2013). Briefly, the method includes solvent protein precipitation of 150 μL serum or plasma and sample filtration using 96-well plates followed by instrumental analyses on an Acquity UPLC coupled to a Quattro Premier XE MS/MS system (Waters Corporation, Milford, USA) operating in negative ionization mode. Fourteen target PFASs (perfluoropentanoic acid, perfluorohexanoic acid, perfluoroheptanoic acid, perfluorooctanoic acid, perfluorononanoic acid, perfluorodecanoic acid, perfluoroundecanoic acid, perfluorododecanoic acid, perfluorotridecanoic acid, perfluorobutane sulfonic acid, perfluorohexane sulfonic acid, linear isomer of perfluorooctane sulfonic acid, perfluorodecane sulfonic acid, and perfluorooctane sulfonamide) were quantified via a matrix matched calibration curve and isotope dilution, where the mean relative response factors (RRFs) obtained from the calibration curve and internal standard response from each sample were used for concentration determination. Eight of the fourteen PFASs detected in the majority (75%) of test subjects were used for further assessment. In this study, we quantified the linear PFOS isomer as an indicator of the change in total PFOS concentrations.

2.3. Quality assurance and quality control

In order to maintain the previously established QA/QC parameters that were validated for rapid analysis of PFASs, the same quality control measures were applied during the subsequent sampling group's extraction and analysis. Quality assurance was maintained by using a matrix matched calibration curve to account for any matrix effects that would influence the analysis. Also, four reference samples from the National Institute for Standards and Technology Standard Reference Material (NIST SRM) 1957 were included per batch (one 96-well plate) in order to verify method accuracy and precision (Table S3). Additionally, QC reference plasma, method blanks, instrument blanks and performance standards were analyzed between every ten samples to test method precision and repeatability (Table S4), determine method detection limits (MDLs) and limits of quantification (LOQs) (Table S5), to monitor instrument and method performance, to ensure no background contamination was present, and to verify acceptable chromatography and signal intensity.

2.4. Data treatment and statistical methods

The first time the PIVUS cohort was sampled, at age 70,1016 people participated. When the cohort turned 75,822 of the original 1016 people were resampled, and when they turned 80 years old, 602 of the 1016 participants were resampled a third time. Following the instrumental analysis of each age group's samples, it was determined that 579 out