Environment International 155 (2021) 106716

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Temporal trends, 2000–2017, of perfluoroalkyl acid (PFAA) concentrations in serum of Swedish adolescents

Erika Norén [a,*], Christian Lindh [a], Anders Glynn [b], Lars Rylander [a], Daniela Pineda [a], Christel Nielsen [a]

[a] Division of Occupational and Environmental Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden
[b] Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden

ARTICLE INFO

Handling Editor: Lesa Aylward

Keywords:
Human Biomonitoring
Population Exposure
Temporal Trends
Perfluoroalkyl Acids
Sample Stability

ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) have been extensively used as surfactants because of their high stability and good water/oil-repellent properties. PFASs, especially perfluoroalkyl acids (PFAAs), have long biological half-lives, and exposure may cause adverse health effects in humans. We assessed temporal trends of concentrations of eight PFAAs in serum of Swedish adolescents (age 16–21 years) from the general population, and estimated the stability of PFAAs and serum samples after 6 years of storage. Repeated cross-sectional sampling was performed on five occasions (covering in total 1213 individuals, 83% males) in southern Sweden between 2000 and 2017. We analyzed serum for perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) using liquid chromatography-tandem mass spectrometry. We assessed time trends using linear regression, long-term stability was assessed by reanalyzing samples collected 2013, and the comparison was done using Pearson correlation and Bland-Altman plots.

PFHxS, PFOS, and PFOA decreased by 6.7% (CI: –7.0, –6.3%), 12.6% (CI: –12.9, –12.3%), and 6.5% (CI: –6.8, –6.1%) per year, respectively, and year of sampling explained 48–81% of the variation in concentrations. PFNA and PFDA seemed to increase up to 2009 and decrease thereafter. The trends were consistent after sensitivity analyses excluding women. Strong correlations of 94–97% were observed for concentrations of all compounds, except PFHxS, after storage. The observed trends closely followed the timing of manufacturers' voluntary phase-out initiatives, and of regulatory measures governing the compounds implemented in the EU and USA. This indicates that these actions mitigated the population's exposure to PFHxS, PFOS, and PFOA and, in recent years, to PFNA and PFDA, in southern Sweden. Furthermore, the results suggest that PFAAs remain stable in serum samples after long-term storage.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are persistent synthetic chemicals for which there is evidence that exposure can cause adverse health effects in humans. The strong carbon–fluorine bond makes PFASs, perfluoroalkyl acids (PFAAs) in particular, very stable and resistant to chemical and biological degradation (Buck et al., 2011; Kissa, 2001). These compounds have been extensively used since the 1950s in various applications to create products that repel water, oil, and dirt and resist high temperatures (Buck et al., 2011; Kissa, 2001). PFASs are mainly used as surfactants in commercial and industrial products such as textiles, paper, food packaging, cookware, outdoor gear, furniture, and firefighting foams (Sunderland et al., 2018).

The general population is mainly exposed to PFAS through food, drinking water, consumer products, indoor air, and dust (D'Hollander et al., 2010; Haug et al., 2011; Schrenk et al., 2020). Very high exposure may also occur through drinking water in areas where water reservoirs close to airports and military bases have been contaminated by fire-fighting foam (Domingo and Nadal, 2019; Gyllenhammar et al., 2015; Kärrman et al., 2011; Li et al., 2018). PFASs are water soluble and, unlike other persistent organic pollutants, do not bind to organic matter to a large degree and can easily migrate from point sources to eventually

* Corresponding author at: Medicon Village, Scheelevägen 8 (Building 402), 223 63 Lund, Sweden.
E-mail address: erika.noren@med.lu.se (E. Norén).

https://doi.org/10.1016/j.envint.2021.106716
Received 28 January 2021; Received in revised form 10 June 2021; Accepted 10 June 2021
Available online 16 June 2021

reach ground- and surface water (Banzhaf et al., 2017).

The high persistence of PFAAs was not discovered until the early 2000s when measurable concentrations of perfluorooctane sulfonic acid (PFOS) were found in wildlife and biota in the Arctic region (McInnis et al., 2017; Routti et al., 2019). In the year 2000, the worldwide manufacturer 3M initiated a phase-out of PFOS and related compounds from their products in agreement with the US EPA (Butenhoff et al., 2006). In 2009, PFOS was also banned in the European Union (European Parliament Directive, 2006) and included in the Stockholm Convention on Persistent Organic Pollutants (SCPOP, 2009). Furthermore, the production and use of perfluorooctanoic acid (PFOA) were phased out by major manufacturers in the USA by 2015. PFOA and its homologs and precursors were included in the Stockholm Convention in 2019 and will be phased out in the EU starting in 2020 (European Parliament Directive, 2017). Despite these measures, concentrations of both PFOS and PFOA are still detected in the environment, biota, and humans because of their persistence and long biological half-lives.

PFAAs mainly bind to serum proteins such as albumin and accumulate in the blood (Chi et al., 2018; Jin et al., 2019). Studies have suggested elimination half-lives in human serum or plasma of around 2–4 years for PFOA, 3–5 years for PFOS, and 5–8 years for perfluorohexane sulfonic acid (PFHxS) (Li et al., 2018; Olsen et al., 2017). Sex-related differences have been observed in the elimination rates, partly explained by increased excretion among women through menstrual bleeding or transfer during pregnancy and breast-feeding (Goralczyk et al., 2015; Harada et al., 2005; Li et al., 2018).

Epidemiological studies have shown associations between levels of PFAAs and health effects in humans. Based on currently available data, the European Food Safety Authority (EFSA) has concluded that decreased antibody response at vaccination in toddlers is the most critical effect (Schrenk et al., 2020). Some previous human biomonitoring studies of PFAAs in populations have assessed changes over time, with results indicating a decrease in concentrations of PFOS and PFOA over the last two decades in various countries (Olsen et al., 2017; Toms et al., 2014). For other PFASs, the reported trend patterns diverge between studies, probably due to differences in the study design, study period, and population composition (Göckener et al., 2020; Kim et al., 2020; Miaz et al., 2020; Wang et al., 2020). Previous studies have not systematically assessed time trends over an extensive period. Studies of well-defined populations with sufficient statistical power are therefore needed to follow up the effects of the actions taken to eliminate environmental pollution from PFASs during the specific period marked by major changes in production and use of these compounds.

Biomonitoring PFAA concentrations in serum provides a reliable measure of the total cumulative exposure from all sources and can be used as a tool for following up the efficacy of legislative efforts to reduce human exposure. Biomonitoring studies often rely on material from biobanks or samples that were collected long ago and that have been stored for several years. Storing serum samples for long periods might impair sample quality and, to some extent, the stability of compounds. Estimates of sample quality, evaporation, and the long-term stability of PFASs in stored samples through reanalysis after storage are therefore of great importance for the reliability and interpretation of such data, although few studies address the issue (Kato et al., 2013).

The main objective of this study was to assess exposure concentrations and temporal trends from 2000 to 2017 of perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) in serum from Swedish adolescents from the general population to estimate the efficacy of the implemented regulatory measures. Furthermore, we addressed the sample integrity and compound stability in serum samples after up to six years of storage.

2. Methods and materials

2.1. Sample collection

We used a repeated cross-sectional study design in which samples were collected on five occasions in 2000, 2004, 2009, 2013, and 2017. Initially, male study participants were recruited through the enrolment for military service in Scania (the southernmost county in Sweden) in 2000 (n = 303), 2004 (n = 200), and 2009 (n = 314) through the National Service Administration in Sweden. Following the decision for the peacetime deactivation of military conscription in Sweden between 2010 and 2017, study participants were then recruited from secondary schools in Scania in 2013 and 2017 and included both males and females (n = 185 and n = 211, respectively). We initially contacted several schools in Scania County about participating in the study, three of which, in Lund (a municipality with 120,000 inhabitants in 2017) and Trelleborg (a municipality with 45,000 inhabitants in 2017), accepted. We performed recruitment and sample collection in the school facilities during the same week. All study participants were 16–21 years old. Two research nurses collected the venous blood samples from the participants. Serum was separated on the same day and transferred from glass sample vials to 2-mL plastic vials, which were stored at –80 °C until analyses. Population characteristics have previously been described elsewhere (Norén et al., 2020).

2.2. Chemical analysis

The analyses of serum samples were performed at the Division of Occupational and Environmental Medicine at Lund University. A modified method previously described by Lindh et al. (2012) was applied. Briefly, serum proteins were precipitated with acetonitrile and centrifuged directly in 96-well plates before analysis. The compounds PFHxS, PFOS, PFHpA, PFOA, PFNA, PFDA, PFUnDA, and PFDoDA were analyzed in the samples using liquid chromatography-tandem mass spectrometry (LC-MS/MS; QTRAP 5500, AB Sciex, Framingham, MA, USA). Two quality-control (QC) samples, four chemical blanks, and calibration standards were included in each sample batch. Concentrations were determined as the total non-isomer-specific compounds. All values were corrected for the chemical blank. The limit of quantification (LOQ) was defined as the mean concentration in the chemical blanks plus ten times the standard deviation of the concentrations corresponding to the peak with the same retention time as the PFAAs in the chemical blanks included in each 96-well plate. The LOQ was determined as 0.1 μg/L for all compounds. All samples were analyzed between 2018 and 2020. For PFHxS, the transitions m/z 399/80 and 399/99 were evaluated, and we consequently used the lower value of the two since possible interferences have been suggested (Chan et al., 2009). Furthermore, the serum samples collected in 2013 were analyzed both in 2014 and 2020 using the same instruments and method with minor improvements, performed by a different lab technician. However, when analyzing PFHxS in 2014, only m/z 399/80 was evaluated and in the comparison of PFHxS concentrations in 2013 samples between analyses in year 2014 and 2020, we therefore only used the 399/80 transition from both analyses. By comparing the concentrations of seven PFAAs in the 2013 samples from the analysis in 2014 and 2020, the long-term stability and sample integrity could be assessed. Details and modifications are presented in Supplementary Material A. The laboratory participates in the ICI/EQUAS exercises for analyses of PFHxS, PFOS, PFHpA, PFOA, PFNA, PFDA, PFUnDA, and PFDoDA and is approved by the HBM4EU project (Supplementary Material B1). In addition, the analyses of PFOS and PFOA were certified by a quality control program between analytical laboratories, coordinated by Professor Hans Drexler at the Institute and Outpatient Clinical for Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg (Supplementary Material B2, B3).

2.3. Statistical analysis

Serum concentrations followed a log-normal distribution and were summarized using non-parametric descriptive statistics for each sampling year and stratified by sex for 2013 and 2017. We assessed pairwise correlations for PFAA concentrations using Spearman's rank-order correlations for 2000 and 2017. Visual assessment of the linearity of time trends was performed using boxplots (log-scale), including the measured concentrations below LOQ. When the boxplots suggested that linearity was plausible, we used linear regression to assess the annual change in serum concentrations by regressing ln-transformed concentrations on calendar year. β coefficients were transformed to percent according to $(\exp(\beta) - 1)^{*}100) = \%change$. We performed residual analyses through visually assessing QQ plots. Concentration outliers were identified as data points with standardized residuals of >3 or <–3. These were considered influential observations and excluded from the model. When the assumption of linearity was violated, we explored quadratic terms that were centered around the mean to avoid collinearity. Some of the observations below LOQ, mainly for PFDA, were still included in the statistical models even though these values have a high level of uncertainty. Applying a method of fixed substitution may dilute the variability of the material, which could affect observations of trends. We did not evaluate trends for compounds for which >30% of the observations were below LOQ. We conducted a sensitivity analysis from which women were excluded. We assessed the stability of the PFAAs in serum and the sample quality after storage for samples collected in 2013 by means of Pearson correlation, comparing the results of the initial analysis in 2014 and those of the reanalysis in 2020 using the same method with minor improvements (Supplementary Material A1). Additionally, we explored the agreement through Bland Altman plots, a methodological approach to quantify the agreement between two analytical measurements (Altman and Bland, 1983). We used the analysis in 2014 as the reference method on the x-axis and plotted it against the relative difference. We plotted (*analysis 2020–analysis 2014/analysis2014 * 100)* on the y-axis (Giavarina, 2015). Limits of agreement were defined as mean difference ± 1.96 STD of percentual difference. The statistical analyses were performed using IBM SPSS Version 24.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Pearson correlation plots of stability and the conversion of estimates to percentages were performed using Microsoft Excel 2011.

3. Results

PFHxS, PFOS, PFOA, PFNA, and PFDA were present in quantifiable concentrations in more than 85% of the samples (Table 1). The boxplots suggested log-linear associations for PFHxS, PFOS, and PFOA (Fig. 1). This was confirmed by the linear regressions, which showed that these three compounds decreased over the sampling period, PFOS by 12.6%, PFOA by 6.5%, and PFHxS by 6.7% per year (Table 2). The variation in concentration explained by sampling year was 81% for PFOS, 58% for PFOA, and 44% for PFHxS. We only observed minor differences of up to 0.5 μg/L in median concentrations of PFOS and PFHxS between males and females (Supplementary Material A2). The linear trends for PFHxS, PFOS, and PFOA were robust and remained after excluding females, with only minor differences in estimates (Supplementary Material A2).

No linear trends were observed for PFNA and PFDA, for which the regression of quadratic terms indicated an inversed u-shaped pattern in serum concentrations over time, with an increase from 2000 to 2009

Table 1
Descriptive statistics for serum concentrations (μg/L) and quantification frequency (%) of perfluoroalkyl acids in adolescents in southern Sweden.

Compound	Year	*n*	% > LOQ	Median (IQR)	95th percentile	Maximum
PFHxS	2000	301	100	1.0 (0.8–1.3)	2.1	37.1
	2004	200	100	0.9 (0.7–1.0)	2.0	8.3
	2009	288	100	0.6 (0.5–0.7)	1.4	10.2
	2013	201	100	0.5 (0.4–0.6)	1.1	11.1
	2017	193	97	0.4 (0.3–0.5)	0.8	1.9
PFOS	2000	300	99	21.4 (17.2–26.5)	38.9	76.9
	2004	200	100	17.2 (14.0–22.3)	34.3	56.9
	2009	288	100	7.0 (5.6–9.0)	13.2	21.5
	2013	201	100	3.4 (2.6–4.5)	6.5	9.1
	2017	195	100	2.6 (1.88–3.6)	6.2	10.2
PFHpA	2000	300	25	0.1 (<LOQ–0.1)	0.2	0.7
	2004	200	37	0.1 (<LOQ–0.1)	0.4	7.4
	2009	288	12	<LOQ (<LOQ–0.1)	0.2	0.5
	2013	201	8	<LOQ (<LOQ–0.1)	0.1	0.5
	2017	195	4	<LOQ (<LOQ–<LOQ)	0.1	0.3
PFOA	2000	300	99	3.6 (2.9–4.4)	6.0	9.7
	2004	200	100	3.0 (2.5–3.8)	5.4	13.3
	2009	288	100	2.5 (2.1–3.0)	4.1	6.1
	2013	201	100	1.7 (1.3–2.1)	3.2	7.9
	2017	195	100	1.1 (0.9–1.4)	1.9	3.1
PFNA	2000	300	99	0.4 (0.3–0.5)	0.7	1.0
	2004	200	100	0.5 (0.4–0.6)	0.9	4.6
	2009	288	100	0.5 (0.4–0.6)	1.0	1.9
	2013	201	100	0.4 (0.4–0.6)	1.0	2.6
	2017	195	100	0.4 (0.3–0.5)	0.7	1.6
PFDA	2000	300	85	0.1 (0.1–0.2)	0.3	0.4
	2004	200	98	0.2 (0.2–0.3)	0.4	1.0
	2009	288	100	0.3 (0.2–0.3)	0.4	0.9
	2013	201	95	0.2 (0.1–0.3)	0.5	1.0
	2017	195	93	0.2 (0.1–0.2)	0.4	0.9
PFUnDA	2000	300	51	0.1 (<LOQ–0.1)	0.2	0.5
	2004	200	70	0.1 (<LOQ–0.2)	0.3	0.4
	2009	288	72	0.2 (<LOQ–0.2)	0.3	0.6
	2013	201	66	0.1 (<LOQ–0.2)	0.3	0.7
	2017	195	65	0.1 (<LOQ–0.2)	0.3	0.7

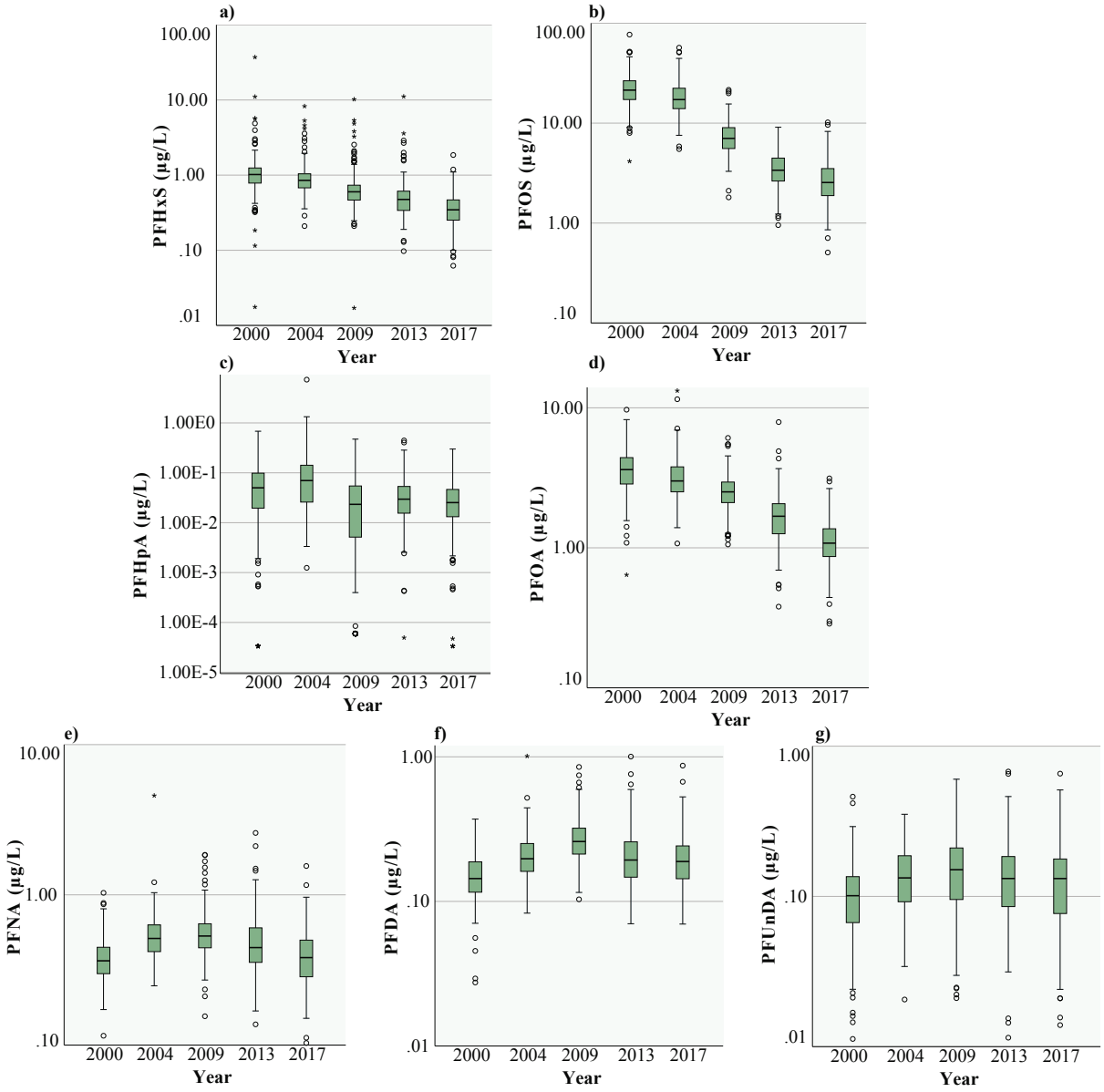

Fig. 1. Serum concentrations of PFAA, concentrations in serum (log-scale) of metabolites: **a** PFHxS, **b** PFOS, **c** PFHpA, **d** PFOA, **e** PFNA, **f** PFDA, and **g** PFUnDA in adolescents in southern Sweden plotted against sampling year.

Table 2
Assessment of temporal trends through linear regression: PFAA (ln-transformed) on calendar year excluding outliers (standardized residual <–3, >3). Regression coefficient (β) and 95% confidence intervals are converted to %.

Compound	*n* total (*n* excluded)	β (%)	95 CI (%)	*p*	R^2
PFHxS	1165 (19)	–6.7	–7.0, –6.3	<0.001	0.48
PFOS	1174 (10)	–12.6	–12.9, –12.3	<0.001	0.81
PFOA	1173 (11)	–6.5	–6.8, –6.1	<0.001	0.58

followed by a decline up to 2017 (Fig. 2). Strong correlations were observed between PFAA in the serum samples, but the pattern of bivariate correlations changed over time (Supplementary Material A2). Trends were not further assessed for PFHpA, PFUnDA, and PFDoDA, as more than 30% of the samples had concentrations below LOQ in multiple sampling years.

In the comparisons between the analyses performed in 2014 and 2020 of samples collected in 2013, the concentrations of PFOS, PFHpA, PFOA, PFNA, PFDA, and PFUnDA correlated very well between analytical batches, with *r* coefficients between 0.94 and 0.99. The correlation of PFHxS concentrations was 0.87. Coefficients of determination were above 94% for all compounds except PFOS (88%) and PFHxS (75%) (Supplementary Material A2). Bland Altman plots showed a minor bias between the analyses 2014 and 2020 varying between −11% and 3% for all compounds, except PFHxS with a mean difference of −18% (Fig. 3). The percentual limits of agreement were generally narrow, except for PFHxS and PFDUnDA. We did not observe any trend in the bias for any compound but a tendency to consistently higher concentrations of PFHxS in the initial analysis 2014.

4. Discussion

Concentrations of PFAAs in serum are in part a measurement of cumulative exposure up to the time of sampling because of very long elimination half-lives. The high detection frequencies of PFHxS, PFOS, PFOA, PFNA, and PFDA indicate widespread PFAA exposure among

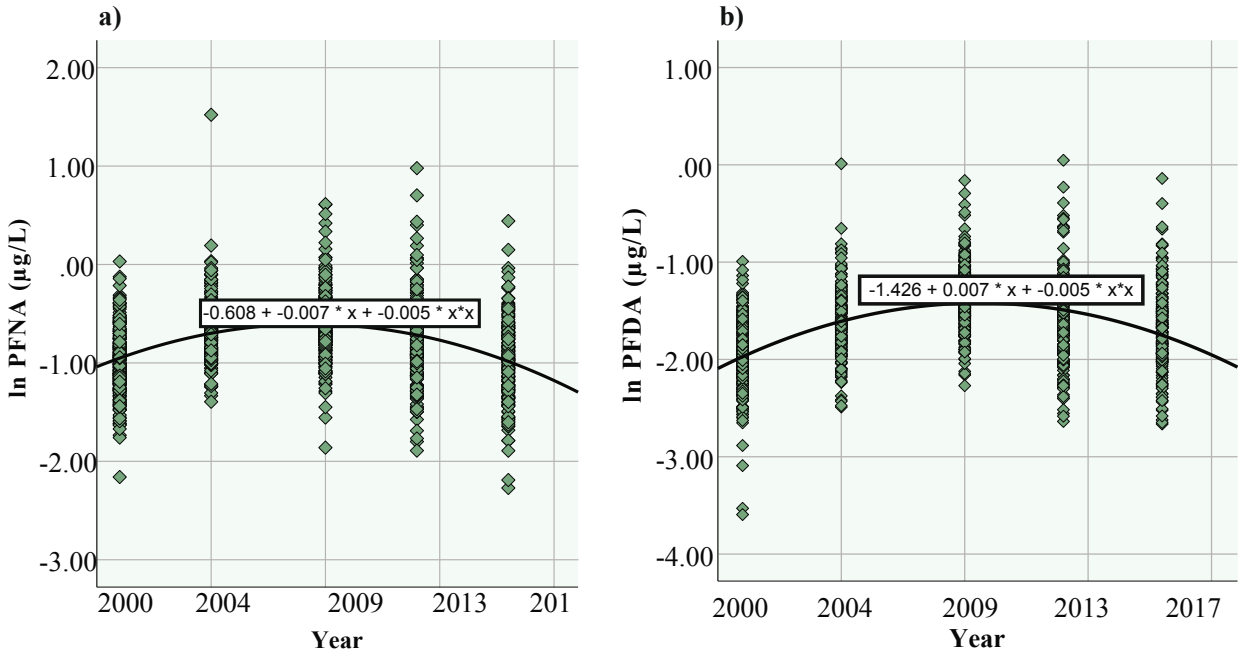

Fig. 2. Assessment of nonlinear trends by regressing quadratic terms of ln-transformed concentrations of **a** PFNA (R^2 = 0.16) and **b** PFDA (R^2 = 0.21) on calendar year.

adolescents in southern Sweden. However, the decreasing trends observed for PFHxS, PFOS, and PFOA demonstrate that important exposure sources of these compounds have been eliminated. Although a delay in the initiation of decreasing trends was observed for PFNA and PFDA, the observed decreasing trends between 2000 and 2017 may, as for PFHxS, PFOS, and PFOA, be related to the voluntary phase-out by industry and to the international regulatory actions taken against PFAS pollution during the same period. The reanalysis of PFAAs in serum samples after six years of storage showed that the sample integrity remains unimpaired and the compounds remain stable, thus being reliable for human biomonitoring of trends in exposure.

4.1. Time Trends, 2000–2017

PFOS was consistently detected at the highest serum concentrations on all sampling occasions, despite being phased out of production by its main manufacturer (3M) in 2002 and restrictions for use being enforced in the EU starting in 2009. The decreasing trends of PFOS show that the phase-out starting in 2002 resulted in decreased body burdens of PFOS in Sweden within a few years. Consequently, our results strongly suggest that important human exposure pathways of PFOS were cut around 2002, although some production continued or began in China after the 3M phase-out (Jiang et al., 2015; Jin et al., 2015). One such important exposure pathway was the use of PFOS and related compounds in food-contact materials. Before the year 2000, about 30% of the PFOS used in the EU was utilized for paper coating (UNEP-POPRC, 2010). Further risk-reducing measures after 2002, such as the inclusion of PFOS in the EU POPs Directive and the Stockholm Convention, ensured that actions were taken against important remaining exposure pathways. A similar pattern and decreasing trend could be observed for PFHxS, likely explained by actions to phase out PFHxS and related compounds taken by the main producer, similar to those taken for PFOS (UNEP-POPRC, 2018). The longer elimination half-life in humans may explain the slower rate of PFHxS decline as compared with PFOS during the studied period (Li et al., 2018).

Serum concentrations of PFOA decreased at a slower rate than did those of PFOS, even though PFOA and related compounds were phased out of production by 3M at the same time as was PFOS. However, many other manufacturers of PFOA remained, which could explain why the 3M phase-out did not have the same immediate impact on serum concentrations of PFOA over time as it did for PFOS and PFHxS. Nevertheless, several of these additional manufacturers later agreed to phase out PFOA and related compounds in agreement with the US EPA through the voluntary PFOA Stewardship Program, which started in 2008 and finished in 2015 (US EPA, 2006). Overall, the year explained a large proportion of the variation in concentrations over time of PFOS, PFHxS, and PFOA in our models, further indicating that the phase-out of production had a significant impact on exposure.

For PFHpA, PFNA, PFDA, and PFUnDA, concentrations were low and temporal trends were less clear. PFNA and PFDA concentrations increased between 2000 and 2009 followed by a decline between 2009 and 2017. Both PFNA and PFDA are long-chain perfluoro-carboxylic acids (PFCAs), together with PFOA included in the PFCA group with eight or more carbons in the molecule ("C8"). The observed decline in serum concentrations after 2009 coincides with the voluntary agreement between the US EPA and several large manufacturers to phase out C8 compounds as grease-proofing agents in paper food contact materials by 2011, along with the revoked approval for the use of these C8 compounds in food contact materials in 2015 (US FDA, 2016, 2019).

Other studies frequently report PFOS as the dominant PFAA detected in serum collected during the same period in US adolescents (Calafat et al., 2007), Faroese adolescents (Grandjean et al., 2017), and US children in 2011 (Gump et al., 2011). Decreasing concentration trends of the phased-out compounds PFOA, PFOS, and PFHxS have been observed in other studies after the year 2000 (Bjerregaard-Olesen et al., 2016; Calafat et al., 2007; Jain, 2018; Nøst et al., 2014; Olsen et al., 2017; Tsai et al., 2018). Diet is considered the main source of exposure in the general population (Domingo and Nadal, 2017), and measurements of decreasing concentrations of PFHxS and PFOS in food items, mainly animal products, in Sweden between 1999 and 2011 are therefore also in line with our findings (Johansson et al., 2014). For PFNA and PFDA, temporal trends of serum concentrations are less consistent over time, with observations of both increasing and decreasing trends, but decreasing trends seem to be consistently reported in studies published after 2010 (Bjerregaard-Olesen et al., 2016; Okada et al., 2013; Olsen et al., 2017; Shu et al., 2019). These observations of decreasing trends

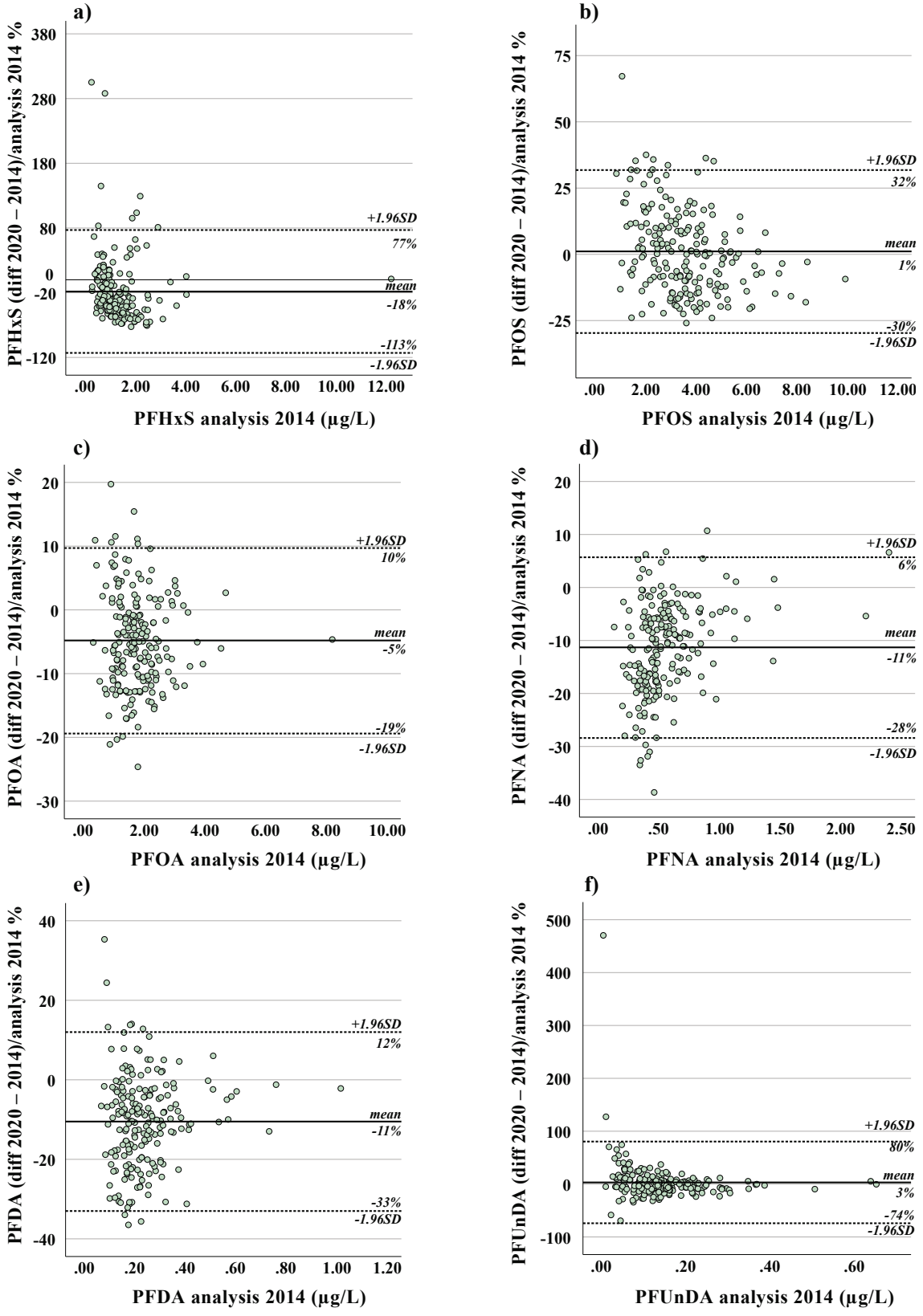

Fig. 3. Agreement of analyses in serum samples before and after 6 years of storage for **a** PFHxS, **b** PFOS, **c** PFOA, **d** PFNA, **e** PFDA, **f** PFUnDA through Bland Altman-plots. Relative difference (%) between measurements on the y-axis and measured concentrations (µg/L) of the reference method in 2014 on the x-axis.

starting around 2010 fit well with the agreement to phase out these compounds between the main manufacturers and the US EPA by 2011 (US FDA, 2016, 2019).

In the year 2000, a strong correlation was observed between PFOS and PFOA concentrations in serum, whereas in 2017, the PFOS concentration was instead strongly correlated with PFDA, PFNA, and PFUnDA concentrations. Correlations indicate common exposure sources and the change in correlation patterns over time suggests that there may have been a shift in exposure sources over time. It could be speculated that food contact materials were common sources of PFOA and PFOS exposure early in the study period, and with the phase-out of these uses, other sources of exposure began to dominate. This is supported by a market basket study by the National Food Agency in Sweden that estimated the per capita intake of PFAAs from different food groups in 2015. For PFOA, cereals dominated the intake, while fish and meat dominated the intake of other long-chained PFCAs and PFOS (National Food Agency, 2017). PFHpA has not been found to a large extent in food items analyzed in Sweden, which could explain the very low or undetectable concentrations in adolescent serum. These results further confirm that the general population is continuously exposed to a mixture of these compounds and that the composition of this mixture changes over time, which needs to be taken into consideration in risk assessments.

To explore whether some exposure to PFOS and PFOA was still ongoing after the phase-out, or whether decreasing temporal trends were due to a complete cessation of exposure, we made a crude comparison of the estimated rates of temporal decline, expressed as temporal trend half-life, and the estimated biological half-lives of PFOS and PFOA in serum at 3.4 years and 2.7 years, respectively, published by Li et al. (2018). The figures and calculations with our transformed data are available in Supplementary Material A2. Based on our median concentrations, the half-lives of the trends in adolescents were estimated to be 5.0 years for PFOS and 9.9 years for PFOA, which is longer than the biological half-lives, suggesting that some exposure to these compounds was still occurring through 2017. The longer temporal trend half-life of PFOA than of PFOS may be due to the slower phase-out of PFOA production than of PFOS production by the main manufacturers outside China.

4.2. Compound stability and sample integrity after storage

The comparisons of PFAA concentrations in the re-analyses performed in 2014 and 2020 of the same samples collected in 2013 showed that concentrations of five of the analyzed PFAAs remained stable in serum samples after storage at –80 °C for up to 6 years, and that the samples did not appear to have evaporated. This was expected based on the stability of the compounds, but this finding also confirms that the analytical method was robust and well validated, yielding very similar results despite being performed by different technicians and on different occasions. The exception was PFHxS and to some extent PFOS, for which there was a lower correlation between the results. We did not observe any trends of relative bias depending on concentrations of PFOS, PFOA, PFNA, PFDA, and PFDUnDA in 2014 in the Bland-Altman plots. The variation between the compounds indicate that it is not likely that the bias is related to the sample integrity. Both PFHxS and PFDUnDA had wider limits of agreement than other compounds. For PFUnDA, this is probably explained by the low concentrations observed, where analytical precision always is a challenge. A similar pattern could be observed for several compounds, that the difference is greater for data points in the lowest concentration range. For PFHxS, it has been suggested that interferences from co-eluting compounds could result in overestimation of the results when only the m/z 399/80 transition is used. Chan et al. (2009) proposed that metabolites from progesterone could interfere in the analysis of PFHxS. Therefore, this comparison of m/z 399/80 of PFHxS should be taken with caution. Furthermore, we analyzed the total non-isomer specific PFOS in this study and there were some indications of interferences for this compound as well, possibly connected to bile acids (Benskin et al., 2007), which could explain the slightly wider limit of agreement observed. Still, no specific pattern was observed for all compounds which indicated that the observed differences did not depend on impaired sample integrity. The observed bias between the analyses are here considered acceptable and in the same range as the coefficients of variation observed in the between-run precision (Supplementary material), considering that the whole method, including sample preparation, analysis, and evaluation, were performed by different technicians 6 years apart. Biobanks consisting of samples stored for several years are important data sources in epidemiological studies, and for assessing changes in exposure over time. It is therefore necessary to continue to evaluate the impact of long-term storage on the quality and reliability of biological samples in biobanks.

4.3. Strengths and limitations

This study comprises repeated cross-sectional measurements of serum concentrations of several PFAAs in adolescents over an extended period of 17 years. Compared with similar studies covering more than 10 years of data, this study was based on a large population that was homogenous in terms of geographic area, number of participants per sample collection, and age of study participants throughout the study period, which is ideal for studying time trends. All samples in the study were analyzed between year 2018 and 2020 using the same instruments and QC samples.

One expected limitation was that the recruitment process changed in the cohorts after 2009 that might affect the trend results, considering previously reported sex-differences in PFAA concentrations (Goralczyk et al., 2015; Harada et al., 2005). Additionally, the recruitment through schools in 2013 and 2017 might have introduced selection bias, with individuals having greater interest in or awareness of chemical exposure being more willing to participate. Still, a strength of our study design is that the possible sex differences were assessed, and that we did not observe any substantial differences in median concentrations or time trends when excluding women from the analyses. Concerning external validity, both the measured concentrations and trend patterns were very similar to findings from other parts of the world. Nevertheless, the comparability of the present results to those in other studies might be limited to studies of similar age groups in Western countries, because of differences in lifestyle factors and the long elimination half-lives of the compounds, and to studies of the general population without additional exposure to PFAAs from contaminated drinking water.

5. Conclusions

We found widespread exposure to PFHxS, PFOS, PFOA, PFNA, and PFDA in Swedish adolescents. Compounds that decreased in serum concentration over time were PFOS by 12.5% per year, PFOA by 6.5%, and PFHxS by 6.0%. PFNA and PFDA displayed an inversed u-shaped pattern over time, with a peak in serum concentrations around 2009, between 2004 and 2013. The observed patterns over time are consistent with the timing of important steps to phase out these compounds by the major manufacturers, the US EPA, and the EU. All trends remained after excluding women from the sensitivity analyses. Year explained a high proportion (R^2 = 44–81%) of the variation in concentrations of PFOS, PFHxS, and PFOA. Furthermore, concentrations of PFOS, PFHpA, PFOA, PFNA, PFDA, and PFUnDA were highly correlated in the same samples analyzed before and after storage, confirming that PFAAs remain stable in stored serum samples for at least 6 years. Our main findings suggest that voluntary and regulatory actions taken to mitigate exposure to specific PFAAs in the USA and EU have had an impact on the exposure in our study population of adolescents in the general population in southern Sweden.

CRediT authorship contribution statement

Erika Norén: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Christian Lindh:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Data curation, Resources, Supervision, Validation, Writing - review & editing. **Anders Glynn:** Conceptualization, Methodology, Supervision, Visualization, Writing - review & editing. **Lars Rylander:** Conceptualization, Methodology, Writing - review & editing. **Daniela Pineda:** Methodology, Validation, Data curation, Writing - review & editing. **Christel Nielsen:** Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Appreciation is expressed to the participants and schools involved in the study. We wish to thank the nurses Else Åkerberg Krook and Ulla Andersson for assistance with sample collection in 2013 and 2017 and the National Service Administration in Sweden, especially Erna Jeppson-Stridsberg, for recruiting participants in the years 2000 to 2009. We would like to thank the laboratory technicians Åsa Amilon and Agneta Kristensen for help with the sample analyses.

Funding

The sample collection and chemical analyses in this work were supported by the Swedish Environmental Protection Agency [grant nos. 215-12-13, 2215-15-005, 2215-16-002, 2215-17-019, and 235-1780-08]. The work was further supported by the Scania County Council and the Faculty of Medicine at Lund University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106716.

References

Banzhaf, S., Filipovic, M., Lewis, J., Sparrenbom, C.J., Barthel, R., 2017. A review of contamination of surface-, ground-, and drinking water in Sweden by perfluoroalkyl and polyfluoroalkyl substances (PFASs). Ambio 46 (3), 335–346. https://doi.org/10.1007/s13280-016-0848-8.

Benskin, J.P., Bataineh, M., Martin, J.W., 2007. Simultaneous characterization of perfluoroalkyl carboxylate, sulfonate, and sulfonamide isomers by liquid chromatography-tandem mass spectrometry. Anal. Chem. 79 (17), 6455–6464.

Bjerregaard-Olesen, C., Bach, C.C., Long, M., Ghisari, M., Bossi, R., Bech, B.H., Nohr, E. A., Henriksen, T.B., Olsen, J., Bonefeld-Jorgensen, E.C., 2016. Time trends of perfluorinated alkyl acids in serum from Danish pregnant women 2008–2013. Environ. Int. 91, 14–21. https://doi.org/10.1016/j.envint.2016.02.010.

Altman, D.G., Bland, J.M., 1983. Measurement in medicine: the analysis of method comparison studies. Statistician 1983 (32), 307–317.

Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., de Voogt, P., Jensen, A.A., Kannan, K., Mabury, S.A., van Leeuwen, S.P., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr. Environ. Assess. Manag. 7 (4), 513–541. https://doi.org/10.1002/ieam.258.

Butenhoff, J.L., Olsen, G.W., Pfahles-Hutchens, A., 2006. The applicability of biomonitoring data for perfluorooctanesulfonate to the environmental public health continuum. Environ. Health Perspect. 114 (11), 1776–1782. https://doi.org/10.1289/ehp.9060.

Calafat, A.M., Wong, L.Y., Kuklenyik, Z., Reidy, J.A., Needham, L.L., 2007. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ. Health Perspect. 115 (11), 1596–1602. https://doi.org/10.1289/ehp.10598.

Chan, E., Sandhu, M., Benskin, J.P., Ralitsch, M., Thibault, N., Birkholz, D., Martin, J.W., 2009. Endogenous high-performance liquid chromatography/tandem mass spectrometry interferences and the case of perfluorohexane sulfonate (PFHxS) in human serum; are we overestimating exposure? Rapid Commun. Mass Spectrom. 23 (10), 1405–1410. https://doi.org/10.1002/rcm.4012.

Chi, Q., Li, Z., Huang, J., Ma, J., Wang, X., 2018. Interactions of perfluorooctanoic acid and perfluorooctanesulfonic acid with serum albumins by native mass spectrometry, fluorescence and molecular docking. Chemosphere 198, 442–449. https://doi.org/10.1016/j.chemosphere.2018.01.152.

D'Hollander, W., de Voogt, P., De Coe, n.W., Bervoets, L., 2010. Perfluorinated substances in human food and other sources of human exposure. Rev. Environ. Contam. Toxicol. 208, 179–215. https://doi.org/10.1007/978-1-4419-6880-7_4.

Domingo, J.L., Nadal, M., 2017. Per- and polyfluoroalkyl substances (PFASs) in food and human dietary intake: a review of the recent scientific literature. J. Agric. Food Chem. 65 (3), 533–543. https://doi.org/10.1021/acs.jafc.6b04683.

Domingo, José L., Nadal, Martí, 2019. Human Exposure to per- and polyfluoroalkyl substances (PFAS) through drinking water: a review of the recent scientific literature. Environ. Res. 177, 108648. https://doi.org/10.1016/j.envres.2019.108648.

European Parliament Directive C/2017/3907. PFOA and its longer chained homologues and chemical precursors (salts and PFOA-related substances) phased out in the EU applicable in July 2020: Commission Regulation (EU) 2017/1000 of 13 June 2017 amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards perfluorooctanoic acid (PFOA), its salts and PFOA-related substances.

European Parliament Directive 2006/122/EC of the European Parliament and of the Council of 12 December 2006. Off J EU, 27 (2006) [L372/32-L372/34, December].

Giavarina, Davide, 2015. Understanding Bland Altman analysis. Biochem Med (Zagreb) 25 (2), 141–151.

Goralczyk, K., Pachocki, K.A., Hernik, A., Strucinski, P., Czaja, K., Lindh, C.H., Jönsson, B.A., Lenters, V., Korcz, W., Minorczyk, M., Matusxak, M., Ludwicki, J.K., 2015. Perfluorinated chemicals in blood serum of inhabitants in central Poland in relation to gender and age. Sci. Total Environ. 532, 548–555. https://doi.org/10.1016/j.scitotenv.2015.06.050.

Grandjean, Philippe, Heilmann, Carsten, Weihe, Pal, Nielsen, Flemming, Mogensen, Ulla B., Budtz-Jørgensen, Esben, 2017. Serum Vaccine antibody concentrations in adolescents exposed to perfluorinated compounds. Environ. Health Perspect. 125 (7), 077018. https://doi.org/10.1289/EHP275.

Gump, B.B., Wu, Q., Dumas, A.K., Kannan, K., 2011. Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition. Environ. Sci. Technol. 45 (19), 8151–8159. https://doi.org/10.1021/es103712g.

Gyllenhammar, I., Berger, U., Sundstrom, M., McCleaf, P., Euren, K., Eriksson, S., Ahlgren, S., Lignell, S., Aune, M., Kotova, N., Glynn, A., 2015. Influence of contaminated drinking water on perfluoroalkyl acid levels in human serum: a case study from Uppsala, Sweden. Environ. Res. 140, 673–683. https://doi.org/10.1016/j.envres.2015.05.019.

Göckener, B., Weber, T., Rüdel, H., Bücking, M., Kolossa-Gehring, M., 2020. Human biomonitoring of per- and perfluoroalkyl substances in German blood plasma samples from 1982 to 2019. Environ. Int. 145, 106123 https://doi.org/10.1016/j.envint.2020.106123.

Harada, K., Inoue, K., Morikawa, A., Yoshinaga, T., Saito, N., Koizumi, A., 2005. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ. Res. 99 (2), 253–261. https://doi.org/10.1016/j.envres.2004.12.003.

Haug, L.S., Huber, S., Becher, G., Thomsen, C., 2011. Characterisation of human exposure pathways to perfluorinated compounds: comparing exposure estimates with biomarkers of exposure. Environ. Int. 37 (4), 687–693. https://doi.org/10.1016/j.envint.2011.01.011.

Jain, R.B., 2018. Time trends over 2003–2014 in the concentrations of selected perfluoroalkyl substances among US adults aged ≥20 years: interpretational issues. Sci. Total Environ. 645, 946–957. https://doi.org/10.1016/j.scitotenv.2018.07.198.

Jiang, W., Zhang, Y., Yang, L., Chu, X., Zhu, L., 2015. Perfluoroalkyl acids (PFAAs) with isomer analysis in the commercial PFOS and PFOA products in China. Chemosphere 127, 180–187. https://doi.org/10.1016/j.chemosphere.2015.01.049.

Jin, H., Zhang, Y., Zhu, L., Martin, J.W., 2015. Isomer profiles of perfluoroalkyl substances in water and soil surrounding a Chinese fluorochemical manufacturing park. Environ. Sci. Technol. 49 (8), 4946–4954. https://doi.org/10.1021/acs.est.5b00212.

Jin, Z., Chi, M., He, Q., Pan, Y., Sun, C., 2019. Perfluoroalkane sulfonyl fluorides non-covalently bind to human serum albumin at Sudlow's sites. Toxicol. Lett. 301, 17–23. https://doi.org/10.1016/j.toxlet.2018.11.001.

Johansson, J.H., Berger, U., Vestergren, R., Cousins, I.T., Bignert, A., Glynn, A., Darnerud, P.O., 2014. Temporal trends (1999–2000) of perfluoroalkyl acids in commonly consumed food items. Environ. Pollut. 188, 102–108. https://doi.org/10.1016/j.envpol.2014.01.026.

Kato, K., Wong, L.-Y., Basden, B.J., Calafat, A.M., 2013. Effect of temperature and duration of storage on the stability of polyfluoroalkyl chemicals in human serum. Chemosphere 91 (2), 115–117. https://doi.org/10.1016/j.chemosphere.2012.11.013.

Kim, Kyunghoon, Bennett, Deborah H., Calafat, Antonia M., Hertz-Picciotto, Irva, Shin, Hyeong-Moo, 2020. Temporal trends and determinants of serum concentrations of per- and polyfluoroalkyl substances among Northern California

mothers with a young child, 2009–2016. Environ. Res. 186, 109491. https://doi.org/10.1016/j.envres.2020.109491.
Kissa, E., 2001. Fluorinated Surfactants and Repellents Vol. 97, 616 pp..
Kärrman, A., Elgh-Dalgren, K., Lafossas, C., Møskeland, T., 2011. Environmental levels and distribution of structural isomers of perfluoroalkyl acids after aqueous fire-fighting foam (AFFF) contamination. Environ. Chem. 8 (4), 372–380. https://doi.org/10.1071/EN10145.
Li, Y., Fletcher, T., Mucs, D., Scott, K., Lindh, C.H., Tallving, P., Jakobsson, K., 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup. Environ. Med. 75 (1), 46–51. https://doi.org/10.1136/oemed-2017-104651.
Lindh, C.H., Rylander, L., Toft, G., Axmon, A., Rignell-Hydbom, A., Giwercman, A., Pedersen, H.S., Góalczyk, K., Ludwicki, J.K., Zvyezday, V., Vermeulen, R., Lenters, V., Heederik, D., Bonde, J.P., Jönsson, B.A., 2012. Blood serum concentrations of perfluorinated compounds in men from Greenlandic Inuit and European populations. Chemosphere 88 (11), 1269–1275. https://doi.org/10.1016/j.chemosphere.2012.03.049.
McInnis, J.J., French, K., Muir, D.C., Spencer, C., Criscitiello, A., De Silva, A.O., Young, C. J., 2017. Emerging investigator series: a 14-year depositional ice record of perfluoroalkyl substances in the High Arctic. Environ. Sci. Process Impacts 19 (1), 22–30. https://doi.org/10.1039/c6em00593d.
Miaz, L.T., Plassmann, M.M., Gyllenhammar, I., Bignert, A., Sandblom, O., Lignell, S., Glynn, A., Benskin, J.P., 2020. Temporal trends of suspect- and target- per/polyfluoroalkyl substances (PFAS), extractable organic fluorine (EOF) and total fluorine (TF) in pooled serum from first-time mothers in Uppsala, Sweden, 1996–2017. Environ. Sci. Process Impacts 22 (4), 1071–1083. https://doi.org/10.1039/c9em00502a.
National Food Agency, 2017. Swedish Market Basket Survey 2015. Report no. 26—2017. 208 pp.
Norén, Erika, Lindh, Christian, Rylander, Lars, Glynn, Anders, Axelsson, Jonatan, Littorin, Margareta, Faniband, Moosa, Larsson, Estelle, Nielsen, Christel, 2020. Concentrations and temporal trends in pesticide biomarkers in urine of Swedish adolescents, 2000–2017. J. Exp. Sci. Environ. Epidemiol. 30 (4), 756–767.
Nøst, T.H., Vestergren, R., Berg, V., Nieboer, E., Odland, J.O., Sandanger, T.M., 2014. Repeated measurements of per- and polyfluoroalkyl substances (PFASs) from 1979 to 2007 in males from Northern Norway: assessing time trends, compound correlations and relations to age/birth cohort. Environ. Int. 67, 43–53. https://doi.org/10.1016/j.envint.2014.02.011.
Okada, E., Kashino, I., Matsuura, H., Sasaki, S., Miyashita, C., Yamamoto, J., Ikeno, T., Ito, Y.M., Matsumara, T., Tamakoshi, A., Kishi, R., 2013. Temporal trends of perfluoroalkyl acids in plasma samples of pregnant women in Hokkaido, Japan, 2003–2011. Environ. Int. 60, 89–96. https://doi.org/10.1016/j.envint.2013.07.013.
Olsen, G.W., Mair, D.C., Lange, C.C., Harrington, L.M., Church, T.R., Goldberg, C.L., Herron, R.M., Hanna, H., Nobiletti, J.B., Rios, J.A., Reagan, W.K., Ley, C.A., 2017. Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000–2015. Environ. Res. 157, 87–95. https://doi.org/10.1016/j.envres.2017.05.013.
Routti, H., Atwood, T.C., Bechshoft, T., Boltunov, A., Ciesielski, T.M., Desforges, J.P., Dietz, R., Gabrielsen, G.W., Jenssen, B.M., Letcher, R.J., McKinney, M.A., Morris, A. D., Riget, F.F., Sonne, C., Styrishave, B., Tartu, S., 2019. State of knowledge on current exposure, fate and potential health effects of contaminants in polar bears from the circumpolar Arctic. Sci. Total Environ. 664, 1063–1083. https://doi.org/10.1016/j.scitotenv.2019.02.030.
Schrenk, D., Bignami, M., Bodin, L., Chipman, J.K., del Mazo, J., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L.R., Leblanc, J.-C., Nebbia, C.S., Nielsen, E., Ntzani, E., Petersen, A., Sand, S., Vleminckx, C., Wallace, H., Barregård, L., Ceccatelli, S., Cravedi, J.-P., Halldorsson, T.I., Haug, L.S., Johansson, N., Knutsen, H. K., Rose, M., Roudot, A.-C., van Loveren, H., Vollmer, G., Mackay, K., Riolo, F., Schwerdtle, T., 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA J. 18, 6223–6391. https://doi.org/10.2903/j.efsa.2020.6223.
Shu, Huan, Lindh, Christian H., Wikström, Sverre, Bornehag, Carl-Gustaf, Ng, Carla A., 2019. Temporal trends and predictors of perfluoroalkyl substances serum levels in Swedish pregnant women in the SELMA study. PLoS ONE 13 (12), e0209255. https://doi.org/10.1371/journal.pone.020925510.1371/journal.pone.0209255.g00110.1371/journal.pone.0209255.t00110.1371/journal.pone.0209255.t00210.1371/journal.pone.0209255.t00310.1371/journal.pone.0209255.t00410.1371/journal.pone.0209255.t005.
Stockholm Convention, 2009. Stockholm Convention on Persistent Organic Pollutants (POPs). SC-4/17: listing of perfluorooctane sulfonic acid, its salts and perfluorooctane sulfonyl fluoride.
Sunderland, E.M., Hu, C.X., Dassuncao, C., Tokranov, A.K., Wagner, C.C., Allen, J.G., 2018. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. J. Exp. Sci. Environ. Epidemiol. 29 (2), 131–147. https://doi.org/10.1038/s41370-018-0094-1.
Toms, L.M., Thompson, J., Rotander, A., Hobson, P., Calafat, A.M., Kato, K., Ye, X., Broomshall, S., Harden, F., Mueller, J.F., 2014. Decline in perfluorooctane sulfonate and perfluorooctanoate serum concentrations in an Australian population from 2002 to 2011. Environ. Int. 71, 74–80. https://doi.org/10.1016/j.envint.2014.05.019.
Tsai, M.-S., Miyashita, C., Araki, A., Itoh, S., Ait Bamai, Y., Goudarzi, H., Okada, E., Kashino, I., Matsuura, H., Kishi, R., 2018. Determinants and temporal trends of perfluoroalkyl substances in pregnant women: the Hokkaido study on environment and children's health. Int. J. Environ. Res. Public Health 15 (5), 989. https://doi.org/10.3390/ijerph15050989.
UNEP-POPRC, 2010. Report of the Persistent Organic Pollutants Review Committee on the work of its sixth meeting: Guidance on alternatives to perfluorooctane sulfonate and its derivates. http://chm.pops.int/Portals/0/download.aspx?d=UNEP-POPS-POPRC.6-13-Add.3-Rev.1.English.pdf.
UNEP-POPRC, 2018. Report of the Persistent Organic Pollutants Review Committee on the work of its fourteenth meeting: Risk profile on perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds.
US EPA, 2006. Fact Sheet: 2010/2015 PFOA Stewardship Program. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program [accessed 11 September 2020].
U.S. FDA. 2016. FDA Revokes Food Additive Approval for the Use of Long-Chain Perfluorinated Compounds as Oil and Water Repellents for Paper Used in Food Packaging. https://wayback.archive-it.org/7993/20171114120118/https://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm479465.htm.
U.S. FDA. 2019. Update on Perfluorinated Grease-proofing Agents. https://www.fda.gov/food/inventory-effective-food-contact-substance-fcs-notifications/update-perfluorinated-grease-proofing-agents.
Wang, Jinghua, Pan, Yitao, Wei, Xiaofei, Dai, Jiayin, 2020. Temporal trends in prenatal exposure (1998–2018) to emerging and legacy per- and polyfluoroalkyl substances (PFASs) in cord plasma from the Beijing Cord Blood Bank, China. Environ. Sci. Technol. 54 (20), 12850–12859. https://doi.org/10.1021/acs.est.0c0187710.1021/acs.est.0c01877.s001.