

*Sakrapport till Naturvårdsverkets Miljöövervakning:*

**Perfluorerade organiska ämnen i serum från förstföderskor i Uppsala – tidstrend 1996-2010**

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## **Perfluoroalkyl substances in serum from first-time mothers in Uppsala – temporal trend 1996-2010**

### **Background**

Perfluorinated alkyl substances (PFASs) are highly fluorinated compounds. Some PFASs are environmentally persistent and possess a strong surface tension lowering potential (Kissa 2001). Manufacturing of some PFASs has spanned over five decades, and they are used in industrial processes (for instance production of fluoropolymers) and in products such as water and stain proofing agents, lubricants, paints and fire-fighting foams (Kissa 2001; Prevedouros et al. 2006). PFASs have been found globally in wildlife (Giesy and Kannan 2001; Houde et al. 2006), and PFASs tend to bind to serum proteins and accumulate in blood and protein rich tissues of exposed organisms (Vanden Heuvel et al. 1991; Jones et al. 2003; Holmstrom and Berger 2008). Increasing chain length of PFASs generally results in increased bioaccumulation (Martin et al. 2003). Human exposure to PFASs is also occurring globally, reflected by the finding of detectable levels of PFASs in human blood in most of the studied areas of the world (Kannan et al. 2004).

The importance of different pathways for human exposure is currently not well understood (Vestergren and Cousins 2009). Intake of contaminated fish has been suggested to contribute significantly to human blood levels of perfluorooctane sulfonate (PFOS) (Berglund et al. 2004; Falandysz et al. 2006; Berger et al. 2009). For PFOS and perfluorooctanoate (PFOA) food is probably an important source of human exposure, although dust in the in-door environment may contribute to the exposure (Haug et al. 2011).

In 2002 the chemical manufacturer 3M completed the phase out of PFOS-related production. The short-chain PFAS perfluorobutane sulfonate was launched as a replacement for PFOS (3M, 2002; Olsen et al. 2008). As a result of the PFOS phase-out, studies of temporal trends of PFAS body burdens in humans have shown that levels of PFOS in human blood have declined since the turn of the century in several areas of the world (Spliethoff et al. 2008; Haug et al. 2009; Sturm and Ahrens 2010). Moreover, levels of PFOA also seem to decline in some parts of the world (Spliethoff et al. 2008; Haug et al. 2009; Sturm and Ahrens 2010). However, little is known about temporal trends of body burdens of other PFASs in humans.

We investigated the temporal trends of perfluorinated carboxylates and sulfonates with carbon chain lengths from 4 to 14 carbons in human blood. The aim was to determine how the phase-out of PFOS-related production has influenced the body burdens of PFASs in humans. Levels of PFASs in pooled blood serum from nursing primiparous women living in the Uppsala area were studied between 1996 and 2010.

## **Material and methods**

### **Recruitment and sampling**

In the POPUP study (Persistent Organic Pollutants in Uppsala Primiparas), first-time mothers from the general population living in Uppsala County were recruited between 1996 and 2010 (N=455). The participants donated a blood sample 3 weeks after delivery. Blood sampling was done using 9 ml Vacutainer® or Vacuette® serum tubes, and serum was stored at -20°C. The study was approved by the local ethics committee of Uppsala University, and the participating women gave informed consent prior to the inclusion in the study.

In this study we used pooled serum samples from the participants for analysis of PFASs. Samples from mothers born in non-Nordic countries (N=10) were not included in the pools. From about 30 women, there was no serum left or the volume was too small to allow inclusion in the pools. The total number of individual samples included in the pools was 413. An effort was made to produce 3 pooled serum samples for each sampling year. 5-25 individual samples were included in each pool (Table 1)

Table 1. Composition of the pooled serum samples used for analyses of PFASs.

Sampling year	N <sup>a</sup>	No of pools	N in each pool	Age (yrs) <sup>b</sup> mean (range)
1996	19	3	6-7	30 (21-41)
1997	62	3	20-21	28 (21-37)
1998	74	3	24-25	29 (21-35)
1999	17	3	5-6	27 (21-31)
2000	20	2	10	30 (21-37)
2001	9	1	9	29 (22-35)
2002	31	3	10-11	30 (24-37)
2004	32	3	10-11	29 (20-34)
2006	30	3	10	30 (19-40)
2007	29	3	9-10	30 (21-39)
2008	30	3	10	29 (20-35)
2009	30	3	10	29 (22-39)
2010	30	3	10	30 (20-41)

<sup>a</sup>Total number of serum samples from the specific sampling year.

<sup>b</sup>Mean age of the women donating blood during the specific sampling year.

### PFAS analyses

Perfluorohexanoate (PFHxA), perfluoroheptanoate (PFHpA), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), perfluorotridecanoate (PFTrDA), perfluorotetradecanoate (PFTeDA), perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorodecane sulfonate (PFDS) and perfluorooctane sulfonamide (FOSA) were analyzed. An aliquot of 0.5 g of human serum was spiked with mass-labeled internal standards <sup>13</sup>C<sub>4</sub>-perfluorooctanoic acid (<sup>13</sup>C<sub>4</sub>-PFOA) and sodium <sup>13</sup>C<sub>4</sub>-perfluorooctane sulfonate (<sup>13</sup>C<sub>4</sub>-PFOS). The serum samples were then extracted (and proteins precipitated) with acetonitrile for 15 min. Following centrifugation at 2000 rpm for 5 min, the supernatant extract was concentrated at 30 °C using nitrogen gas. The extract was cleaned-up using graphitized carbon (Supelclean ENVI-Carb 120/400, Supelco, Stockholm, Sweden) and glacial acetic acid. After centrifugation at 10,000 rpm for 10 min the clear supernatant was transferred to an autoinjector vial. Aqueous ammonium acetate (4 mM) and the volumetric standard 3,5-bis(trifluoromethyl)phenyl acetic acid were added.

Instrumental analyses were performed on a high performance liquid chromatography system (Waters Acquity) coupled to a high resolution mass spectrometer Q-ToF Premier (Micromass) (HPLC/HRMS). A C18 column was used in order to trap and delay PFCA

contamination from the HPLC system, and was placed in the solvent line immediately before the sample injector. The target compounds were separated on an Acquity BEH C18 column (Waters) using a methanol/acetonitrile/water gradient buffered with ammonium acetate and 1-methyl piperidine.

Quantification was performed using the internal standard method. Procedural blank extraction experiments were performed to determine the method detection limits (MDLs) and quantification limits (MQLs). MDLs ranged between 0.01 and 0.25 ng/g and MQLs were approximately a factor 3 higher than the corresponding MDLs. The background in sample extract chromatograms was not elevated compared to blank extracts. Matrix spike extraction experiments were performed for all analytes and individual recoveries ranged between 66 and 90%. Recoveries of the internal standards from the sample set were on an average ( $\pm 1$  standard deviation)  $91\pm 13\%$  for  $^{13}\text{C}_4$ -PFOA and  $82\pm 14\%$  for  $^{13}\text{C}_4$ -PFOS. The average recoveries of all detected analytes deviated  $<13\%$  from the average recovery of their respective internal standard compound. A human serum sample previously used in an international interlaboratory comparison study in 2006 (van Leeuwen et al. 2006) was analyzed four times along with four different batches of samples. The average quantified concentrations ( $n=4$ ) deviated by  $<5\%$  from the median concentration obtained in the interlaboratory comparison study for PFOA, PFNA and PFOS.

### **Calculations and statistics**

To test for significant changes in the individual PFAS concentrations over time, log-linear regression analyses on the geometric means for the pooled samples, analyzed each year, (13 years) were carried out. To test for non-linear trend components, a running mean smoother was applied. Analysis of variance (ANOVA) was used to test this line for significance.

Table 2. Levels of PFASs in 36 pooled samples of blood serum from first-time mothers in Uppsala (ng/g fresh weight). For levels <MQL (method quantification limit), the actual determined value is given *in italics*. Levels below the MDL (method detection limit) are given as <MDL

Year	PFBS	PFHxS	PFOS	PFDS	FOSA	PFHpA	PFOA	PFNA	PFDA	PFUnDA
1996	<0.013	1.65	22.7	0.137	0.793	<i>0.075</i>	2.18	0.499	<i>0.177</i>	0.207
1996	<i>0.014</i>	2.50	27.3	0.042	0.572	<i>0.078</i>	2.92	0.412	0.207	0.232
1996	<i>0.021</i>	2.29	23.3	0.260	0.507	<i>0.084</i>	2.69	0.536	0.235	0.178
1997	<i>0.029</i>	2.35	24.8	0.089	0.610	<i>0.100</i>	3.07	0.400	0.257	0.250
1997	<0.013	1.59	20.3	0.153	0.602	<i>0.114</i>	2.26	0.275	0.246	0.169
1997	<0.013	1.67	20.7	0.148	0.441	<i>0.080</i>	2.54	0.468	0.260	0.286
1998	<0.013	1.19	20.2	<i>0.021</i>	0.477	<i>0.073</i>	2.22	0.419	0.220	0.184
1998	<0.013	2.03	23.1	0.166	0.410	<i>0.140</i>	2.66	0.467	0.252	0.244
1998	<i>0.019</i>	2.24	21.0	0.044	0.514	<i>0.084</i>	2.35	0.439	0.233	0.221
1999	<0.013	2.05	20.0	<i>0.020</i>	0.512	<i>0.061</i>	2.38	0.332	<i>0.151</i>	0.167
1999	<0.013	3.02	21.5	0.046	0.584	<i>0.056</i>	3.11	0.431	0.169	0.287
1999	<i>0.013</i>	1.84	23.0	<i>0.022</i>	0.572	<i>0.118</i>	2.49	0.413	0.193	0.158
2000	<i>0.018</i>	2.45	18.7	0.048	0.363	<i>0.063</i>	2.65	0.377	<i>0.193</i>	0.217
2000	<0.013	3.10	22.0	0.052	0.441	<i>0.094</i>	2.50	0.410	<i>0.191</i>	0.220
2001	<i>0.017</i>	2.00	28.1	0.057	0.572	<i>0.110</i>	3.05	0.650	0.294	0.350
2002	<i>0.025</i>	2.30	17.0	0.064	0.185	<i>0.079</i>	2.17	0.377	0.202	0.250
2002	<i>0.016</i>	3.11	18.7	<i>0.037</i>	0.282	<i>0.132</i>	2.59	0.501	0.248	0.298
2002	<0.013	2.93	23.2	0.048	0.301	<i>0.087</i>	2.98	0.526	0.297	0.300
2004	<i>0.029</i>	2.21	16.0	<i>0.037</i>	<i>0.073</i>	<i>0.102</i>	2.12	0.530	0.290	0.332
2004	<i>0.026</i>	3.91	16.6	0.051	0.205	<i>0.097</i>	2.12	0.506	0.328	0.327
2004	<0.013	1.89	13.6	0.052	<i>0.105</i>	<i>0.107</i>	2.15	0.460	0.317	0.197
2006	0.069	3.96	16.5	0.043	<i>0.101</i>	<i>0.089</i>	2.11	0.612	0.308	0.263
2006	0.043	5.38	12.2	<i>0.026</i>	<0.040	<i>0.093</i>	1.89	0.461	0.273	0.192
2006	<i>0.033</i>	3.31	10.7	<i>0.025</i>	<0.040	<i>0.080</i>	1.70	0.445	0.282	0.264
2007	<i>0.037</i>	4.58	15.1	0.057	<i>0.071</i>	<i>0.090</i>	2.41	0.806	0.322	0.268
2007	<i>0.034</i>	4.79	18.3	<i>0.022</i>	<i>0.078</i>	<i>0.065</i>	2.42	0.590	0.319	0.246
2007	<i>0.026</i>	3.27	8.80	<i>0.023</i>	<i>0.056</i>	<i>0.064</i>	1.36	0.537	0.223	0.203
2008	0.052	5.16	11.1	<i>0.021</i>	<0.040	<i>0.114</i>	2.01	0.852	0.211	0.228
2008	0.061	4.01	9.25	<i>0.024</i>	<i>0.049</i>	<i>0.058</i>	1.69	0.533	0.306	0.278
2008	0.065	4.21	10.4	<i>0.039</i>	<0.040	<i>0.082</i>	2.58	0.924	0.429	0.287
2009	0.086	4.19	6.64	<i>0.024</i>	<0.040	<i>0.106</i>	1.64	0.743	0.349	0.310
2009	0.054	4.58	7.19	<i>0.027</i>	<0.040	<i>0.080</i>	2.13	0.799	0.386	0.292
2009	0.094	6.15	7.54	<i>0.037</i>	<0.040	<i>0.119</i>	1.77	0.748	0.294	0.312
2010	0.074	6.16	6.25	<i>0.035</i>	<0.040	<i>0.135</i>	2.17	1.00	0.482	0.353
2010	0.092	5.63	5.00	<i>0.011</i>	<0.040	<i>0.094</i>	1.64	0.777	0.312	0.298
2010	0.108	8.50	6.44	<i>0.020</i>	<0.040	<i>0.084</i>	1.56	0.615	0.325	0.211

## Results and Discussion

Concentrations of PFASs in the serum pools are shown in table 2. The concentrations of PFHxA, PFDoDA, PFTTrDA and PFTTeDA were <MDL in all samples. We observed diverging temporal trends of the PFASs studied, with some showing increasing levels during the study period, whereas others showed decreasing or unchanged levels (Table 3, Figure 1, 2 and 3). Increasing levels between 1996 and 2010 were observed for PFBS ( $p<0.001$ ), PFHxS ( $p<0.001$ ), PFNA ( $p<0.001$ ), and PFDA ( $p<0.001$ ), whereas levels for PFOS ( $p<0.001$ ), PFDS ( $p<0.001$ ), FOSA ( $p<0.001$ ) and PFOA ( $p<0.001$ ) decreased (Table 3). No significant temporal trends for PFHpA and PFUnDA were observed. However, for these two analytes most results were below or very close to the respective MQLs.

The decrease in FOSA, PFOS, and PFDS is most probably a reflection of the phase-out of PFOS-related production, which according to the main manufacturer 3M was completed in 2002 (3M 2011). The concomitant increase in PFBS levels may be a result of the introduction of this short-chain PFAS as a replacement for PFOS (3M 2002a; Olsen et al. 2003). To our knowledge, no study has reported a temporal increase in PFBS levels in blood serum during the last decade. This may at least partially be due to higher MDLs in earlier studies (Haug et al. 2009; Wilhelm et al. 2009).

The mean PFBS level increased with 14% per year among the young Swedish women (Table 3). It has been proposed that PFBS has a much lower potential for bioaccumulation in humans than PFOS due to a much shorter half-life of PFBS in human serum (Olsen et al. 2007; Olsen et al. 2009). Our results suggest that the population of young Swedish women have experienced a rapid increase of PFBS exposure during the last decade.

Reports from Norway, USA, and Japan have also shown a relatively rapid decline in PFOS levels in blood serum during the last decade (Jin et al. 2007; Spliethoff et al. 2008; Sturm and Ahrens 2010; Haug et al. 2011). Within the population of young women living in Sweden during the period 1996 to 2010 average blood serum levels of PFOS decreased with 9% per year. This relatively rapid decline in blood levels indicates that a major source of human PFOS exposure was eliminated by the phase-out of PFOS-related production.

Table 3. Annual change in concentrations of PFASs in blood serum, 1996–2010<sup>a</sup>.

Compound	N	Change per year (%)		R <sup>2</sup> (%)	p
		mean	95% CI		
			Lower/upper		
<b>PFBS</b>	36	14	9.9/17	85	<0.001
<b>PFHxS</b>	36	8.3	6.2/10	88	<0.001
<b>PFOS</b>	36	-9.1	-12/-6.2	82	<0.001
<b>PFDS</b>	36	-9.5	-14/-5.1	67	<0.001
<b>FOSA</b>	36	-26	-30/-21	93	<0.001
<b>PFHpA</b>	36	ns			
<b>PFOA</b>	36	-3.0	-4.3/-1.8	72	<0.001
<b>PFNA</b>	36	4.6	2.5/6.7	69	<0.001
<b>PFDA</b>	36	3.8	1.8/5.7	63	<0.001
<b>PFUnDA</b>	36	ns			

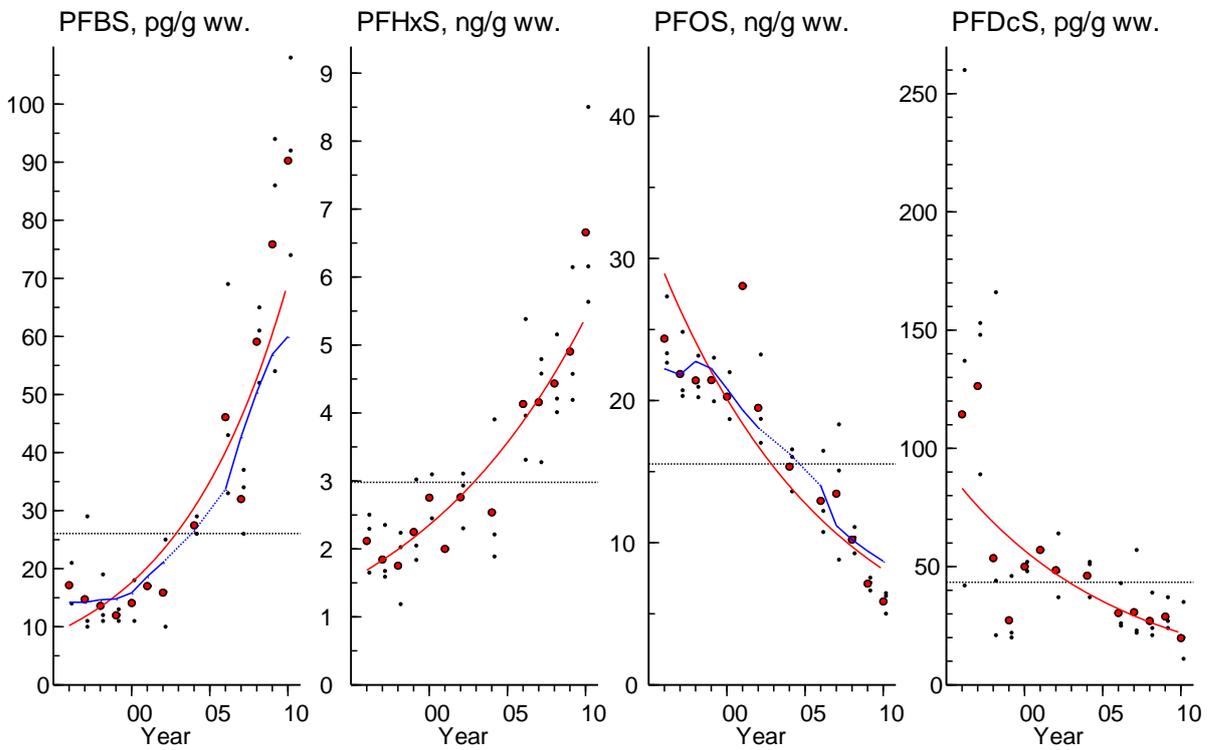
<sup>a</sup>CI=confidence interval, ns=not significant.

PFHxS levels increased among the Swedish women (Table 3, Figure 1). In humans, the half-life of PFHxS is longer than the half-lives of PFOS and PFOA (Olsen et al. 2007). It may be possible that some of the differences in temporal trends of PFOS and PFHxS are due to the higher persistence of PFHxS. However, a temporal increase of PFHxS levels has also been reported in blood plasma from young German adults between 1975 and 2004 (Wilhelm et al. 2009). An exponential increase in PFHxS levels was also observed during the period 1972–2000 in pooled mother’s milk samples from young Swedish women from the Stockholm area (Sundstrom et al. 2011). Between 2001 and 2008, however, no significant trend could be detected. During this time period only 6 pooled samples were analysed, giving a low statistical power to detect trends. This may also be the reason why Kärroman et al. (Karrman et al. 2007) did not find any temporal trends in PFAS levels in a few pooled mother’s milk samples from the POPUP study between 1996 and 2000. Among middle-aged men from Norway, no temporal trend of PFHxS could be seen between early 1990s and 2006 (Haug et al. 2009). In contrast to our finding, PFHxS levels in whole blood decreased between 2000 and 2007 among infants from New York State, USA, with a disappearance half-life of 8.8 years (CI 5.5–16.2 years) (Spliethoff et al. 2008). The differences in temporal trends of PFHxS between young women from Sweden and infants from the USA may be due several factors, such as differences in use of PFASs in consumer products between Sweden and the USA or differences in use of PFAS-containing consumer products in the countries. Moreover, there may be age-related differences in exposure patterns.

According to 3M, PFHxS was a residual by-product in the production of perfluorohexane sulfonyl fluoride (PHFS), which has been used in fire fighting foams and post-market carpet treatment applications (3M 2002b). A case report from Canada, strongly suggests that humans may be exposed to PFHxS from consumer products (Beesoon et al. 2010). Moreover, analyses of dust from cars, homes, work places and schools suggest that dust may be a source of PFHxS exposure, especially in high dust ingestion scenarios (Goosey and Harrad 2011). The similarity of the trends of PFBS and PFHxS may also suggest PFHxS to be a by-product in the current PFBS-related production. However, we analyzed two PFBS products (Fluka and Dyneon) and did not find any traces of PFHxS.

Among the perfluorinated carboxylates studied by us, PFNA, and PFDA showed increasing temporal trends in blood serum between 1996 and 2010, whereas levels of PFOA decreased slowly (Table 3, Figure 3). This suggests a shift in the use of perfluorinated carboxylates towards longer carbon chains. A phase-out of PFOA has been initiated by some manufacturers (EPA 2010), and the declining PFOA exposure of young Swedish women is most probably a result of this phase-out. The long-chain carboxylic acids may derive from PFNA-related products or from degradation of precursors such as fluorotelomer alcohols, which are still in production.

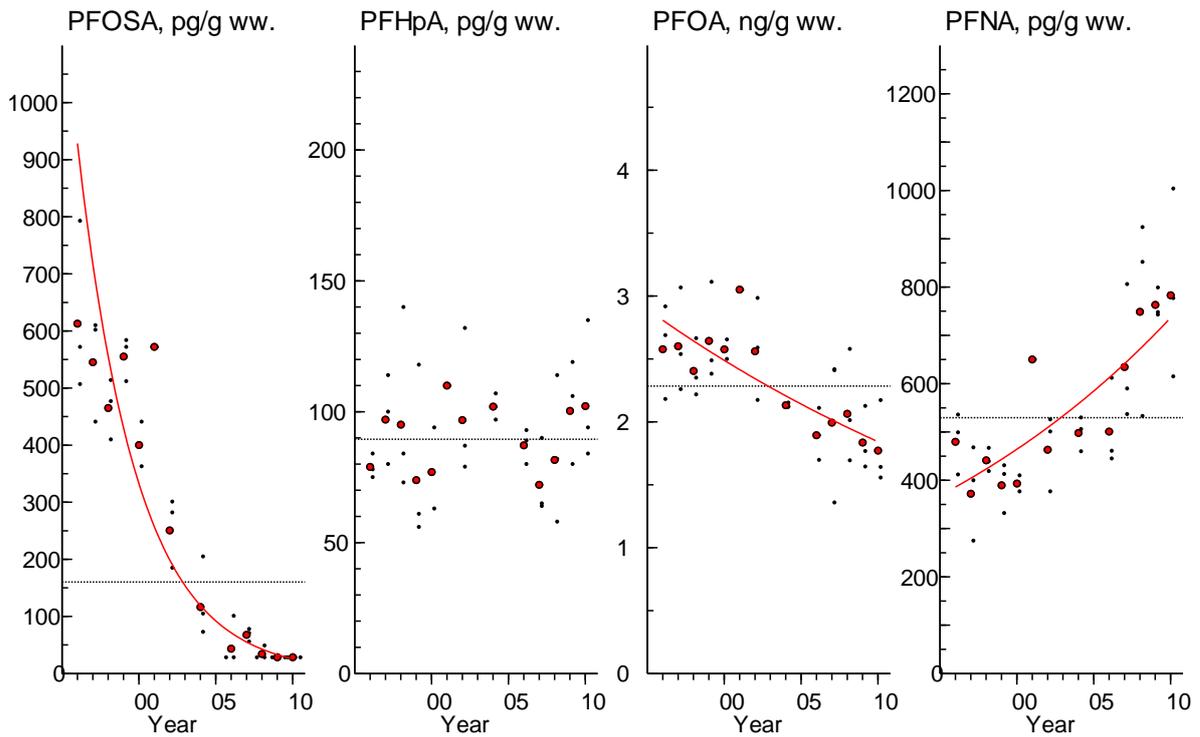
## PFC's in human blood serum



Source: SLV, Anders Glynn 11.03.28 23:05, PFAS1\_u

Figure 1. Concentrations of perfluorinated alkyl sulfonates in pooled samples (N=36) of blood serum from first-time mothers in Uppsala sampled between 1996 and 2010. The bigger red dots represents the geometric means for the pooled samples for each year. The red regression lines show significant linear trends for log-normal PFAS data. A running mean smoother (blue line) shows significant non-linear trend components. PFC's=perfluoroalkyl compounds, PFDcS=PFDS.

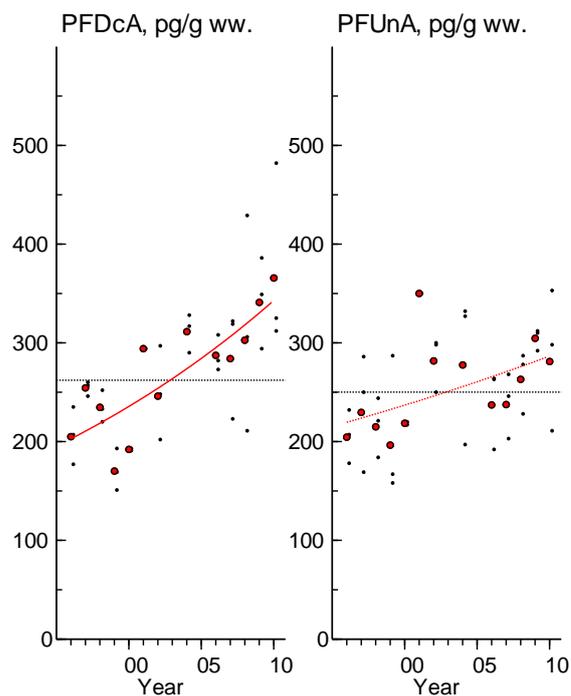
## PFC's in human blood serum



Source: SLV, Anders Glynn 11.03.28 23:17, PFAS2\_u

Figure 2. Concentrations of perfluorooctane sulfonamide and perfluorinated alkyl carboxylates in pooled samples (N=36) of blood serum from first-time mothers in Uppsala sampled between 1996 and 2010. The red regression lines show significant linear trends for log-normal PFAS data. The red regression lines show significant linear trends for log-normal PFAS data. PFC's=perfluoroalkyl compounds, PFOSA=FOSA

## PFC's in human blood serum



Source: SLV, Anders Glynn 11.03.28 23:21, PFAS3\_u

Figure 2. Concentrations of perfluorinated alkyl carboxylates in pooled samples (N=36) of blood serum from first-time mothers in Uppsala sampled between 1996 and 2010. The red regression lines show significant linear trends for log-normal PFAS data. The red regression lines show significant linear trends for log-normal PFAS data. PFC's=perfluoroalkyl compounds, PFDCa=PFDA, PFUnA=PFUnDA.

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