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Temporal trends of poly- and perfluoroalkyl substances (PFASs) in serum from children at 4, 8, and 12 years of age, in Uppsala 2008-2015

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Sammanfattning
Projektet undersökte om halterna av 13 poly- och perfluorerade alkylsubstanser (PFAS) i blodserum förändrats med tiden bland 4-, 8- och 12-åriga barn från Uppsala provtagna under perioden 2008-2015. PFAS är kemikalier som har stor användning i konsument- och kemikalieprodukter. Barnen rekryterades och provtogs i en uppföljning av PFAS-exponeringen 4, 8 eller 12 år efter att de fötts. Barnens mammor deltog, vid barnens födelse, i en undersökning av gravida och ammande kvinnors exponering för miljöföroreningar som genomförs av Livsmedelsverket, med finansiering av Naturvårdsverkets Hälsorelaterade miljööövervakning. Uppföljningen av barnen har godkänts av den regionala etikprövningsnämnden i Uppsala och barnens mammor har gett skriftligt samtycke gällande barnens deltagande. De undersökta PFAS kan delas upp i två grupper: karboxylsyror och sulfonsyror. Resultaten visar att tidstrenderna varierar beroende på vilken substans som undersökts. Bland karboxylsyrorna minskade halterna av PFHpA (7,6 %/år), PFOA (7,2 %/år) och PFDA (4,1 %/år), medan halterna av PFUnDA ökade (3,4 %/år). Bland sulfonsyrorna minskade PFOS (5,6 %/år) medan PFHxS ökade (8,1 %/år). För vissa substanser varierade trenden beroende på var barnen bodde vid provtagning. Vissa delar av Uppsala har haft förorenat dricksvatten fram till 2012. En uppdelning av barnen gjordes beroende på om de bodde i ett område som fått eller inte fått förorenat vatten. Denna uppdelning visade att PFHpA sjönk bland barn som inte fått förorenat vatten men var oförändrad hos barn som fått förorenat vatten. Minskningen av PFOS gick snabbare bland barn som inte fått förorenat vatten och ökningen av PFHxS gick snabbare bland barn som fått förorenat vatten. Detta visar att exponeringen från dricksvatten påverkade hur halterna av dessa PFAS förändrades bland barn under studieperioden.

Temporal trends of poly- and perfluoroalkyl substances (PFASs) in serum from children at 4, 8, and 12 years of age, in Uppsala 2008-2015

Background

In recent years, poly- and perfluorinated alkyl substances (PFASs) have attracted much attention as emerging environmental health risks to wildlife and humans around the world. Although production and use of PFASs has been ongoing for many decades, research on environmental pollution and human exposure is nascent. Concerns around these substances started in the year 2000 following the announcement that the main manufacturer of perfluorooctane sulfonate (PFOS) and related compounds, 3M, would phase-out production within a few years (EPA 2000). 3M took action after it was revealed that PFOS displayed relatively high toxicity and was globally distributed in humans and wildlife. Moreover, in 2006 the main manufacturers of perfluorooctanoic acid (PFOA) and related compounds agreed with the United States Environmental Protection Agency (US EPA) to voluntarily phase-out production of PFOA by 2015 (EPA 2015). PFOS and PFOA are alkyl acids with a full substitution of fluorine atoms on the carbon chain. Perfluoroalkyl chains display considerable chemical and thermal stability, along with amphipathic properties (Buck, Franklin et al. 2011), while the presence of polar functional groups (i.e. COO^- or SO_3^-) imparts considerable water solubility.

Human exposure to PFOS and PFOA is ongoing due to decades of pollution arising from use of these substances. While blood serum/plasma levels of PFOS and PFOA have decreased in many areas of the world since the phase-out, levels of other PFASs have continued to increase (Glynn, Berger et al. 2012; Nost, Vestergren et al. 2014).

Although the fluorochemical industry has moved away from production of PFOS, PFOA and related compounds, a recent study by the Swedish Chemicals Agency recently determined that thousands of PFASs are in circulation on the global market (KEMI 2015). PFASs with longer carbon chains (i.e. C7 and longer), such as PFOS and PFOA, have been replaced with shorter chain PFASs mainly with six perfluorinated carbons. A considerable increase in both the number and diversity of proposed uses was suggested based on patent information (KEMI 2015).

PFASs are incorporated into class B fire-fighting foams used for extinction of fires involving highly flammable liquids (Moe, Huber et al. 2012). In many parts of the world, the

use of PFAS-containing fire-fighting foam during training of fire-fighting personnel has led to contamination of soil as well as surface and ground waters with PFASs (Filipovic, Woldegiorgis et al. 2015; Anderson, Long et al. 2016). In Sweden, high PFOS levels were found in ground water in close vicinity to the fire-fighting training area of two commercial airports in 2009 (Samuelsson, Sander et al. 2009; Ahrens, Norstrom et al. 2015). In 2011, high levels of PFOS, PFOA and perfluorohexane sulfonate (PFHxS) were observed in drinking water in an area of the capital Stockholm, caused by leakage from a suspended Swedish Air Force Base (Filipovic, Woldegiorgis et al. 2015). This was followed by several reports of contamination around fire-fighting training areas all over Sweden, prompting the Swedish National Food Agency (SNFA) in 2014 to issue an action limit of 90 ng/l for PFASs in drinking water based on the sum of 7 PFASs. In 2016 this limit was extended to 11 PFASs (Livsmedelsverket 2016).

A large portion of the population in the City of Uppsala, Sweden, has consumed PFAS-contaminated water and contamination has been ongoing for at least 20 years (Gyllenhammar, Berger et al. 2015). Due to the long distance between the drinking water production wells and the polluted fire-fighting training site, the sum PFAS levels in the wells are only slightly above the SNFA action limit of 90 ng/l (Gyllenhammar, Berger et al. 2015). Sampling of ground water in the Uppsala aquifer close to the training site showed levels above 1000 ng/l. In 2012 the contamination was discovered and the affected production wells were closed. Continuous PFAS measurements 2012-14 in contaminated production well water showed PFAS levels decreasing in the order PFHxS > PFOS > PFBS ~ PFHxA (Gyllenhammar, Berger et al. 2015). As a consequence of the contaminated drinking water, increased levels of PFHxS were observed in primiparous Uppsala women sampled between 1996 and 2012 (Gebbink, Glynn et al. 2015). Women living in areas receiving the contaminated water also had higher levels of PFBS and PFHxA (Gyllenhammar, Berger et al. 2015), but not of PFOS, indicating that drinking water had been a significant source of exposure to the former two PFAAs, but not to the latter.

The women in the Uppsala cohort had in many cases only lived in Uppsala for a few years, and some had most probably moved around in the city. Exposure may also have varied due to the women having daily activities (education or work) in other parts of the city than where they lived. However, their children most likely did not move around as much and often have their daily activities (e.g. day care and school) in the same area as where they live.

The aim of our study was to determine temporal trends of PFASs in the POPUP children, and to investigate if trends vary depending on the area of living.

Table 1. Personal characteristics of the participating children.

Age category	Variable		n	Mean	Median	Range
4	Age (year)		57	3.9	3.9	3.3 – 5.1
	Weight (kg)		57	17	17	13 – 23
	Length (cm)		57	102	103	93 – 105
	Variable		**n**	**%**		
	Sex	Female	21	37		
		Male	36	63		
	City district	Outside of Uppsala	20	35		
		District 1	14	25		
		District 2	2	4		
		District 3	21	37		
Age category	**Variable**		**n**	**Mean**	**Median**	**Range**
8	Age (year)		55	8.4	8.3	7.3 – 9.6
	Weight (kg)		54	29	28	20 – 44
	Length (m)		54	132	131	110 – 150
	Variable		**n**	**%**		
	Sex	Female	21	38		
		Male	34	62		
	City district	Outside of Uppsala	33	60		
		District 1	8	15		
		District 2	1	2		
		District 3	13	24		
Age category	**Variable**		**n**	**Mean**	**Median**	**Range**
12	Age (year)		119	12.2	12.2	11.1 – 13.2
	Weight (kg)		113	44	43	28 – 67
	Length (m)		118	154	154	136 – 176
	Variable		**n**	**%**		
	Sex	Female	56	47		
		Male	63	53		
	City district	Outside of Uppsala	66	55		
		District 1	15	13		
		District 2	4	3		
		District 3	34	29		

Material and methods

Recruitment and sampling

First-time mothers were randomly recruited during pregnancy (1996-99) or shortly after pregnancy (2000-2015). In 2008 a follow-up study on the mothers and their first-born children was initiated. The mothers answered a self-administered questionnaire about dietary habits and other life-style factors (Table 1), and health of the mother and child (age 12, N=289; age 8-9, N=131; age 4, N=202). A nurse took blood samples from the children at home (age 12, N=121, age 8-9, N=56; age 4, N=78) using 9 ml Vacutainer® or Vacuette®

serum tubes and serum was stored at -20°C. The study was approved by the local ethics committee in Uppsala, Sweden, and the participating women gave informed consent prior to the inclusion of the children in the study.

PFAS analyses

PFASs (Table 2) were analyzed in 57 samples from 4 year old children, 55 samples from 8-9 year old children and 119 samples from 12 year old children as described in Gyllenhammar et al. (2015). In short, 0.5 g serum was spiked with internal standards and extracted with acetonitrile in an ultrasonicating bath. The concentrated extract underwent dispersive clean-up with graphitized carbon. Aqueous ammonium acetate and volumetric standards were added before instrument analysis on an Acquity ultra performance liquid chromatography system (UPLC) coupled to a Xevo TQ-S tandem mass spectrometer (MS/MS (both Water Corp., Milford, MA, U.S.) operated in negative electrospray ionization, multiple reaction monitoring mode. The instrumental method including optimized parameters is described in detail in Vestergren et al. (2012). Quantification was performed by isotope dilution using a 5-point calibration curve (linear, 1/x weighting) which was run before and after samples. For most targets, exactly matched isotopically labelled internal standards were available. For PFBS, PFTriDA, PFTeDA, and PFPeDA, a structurally similar internal standard was used (Table 2). For PFHxS and PFOS, branched and linear isomers were quantified separately. The Method quantification limits (MQLs) were 0.16 ng/g serum for PFHxA; 0.08 ng/g for PFHpA; 0.8 ng/g for PFOA; 0.08 ng/g for PFNA, 0.10 ng/g for PFDA and PFUnDA, 0.08 for PFDoDA; 0.02 ng/g for PFTriDA, 0.06 ng/g for PFTeDA; 0.1 ng/g for PFPeDA, 0.01 ng/g for PFBS, 0.01 ng/g for PFHxS; and 0.01 ng/g for PFOS.

Table 2. PFASs included in the study.

Substance	No of carbons in fluorinated chain	Abbreviation	Internal Standards
Perfluoroalkyl sulfonic acids (PFSA)			
Perfluorobutane sulfonic acid	4	PFBS	$^{18}O_2$-PFHxS
Perfluorohexane sulfonic acid[a]	6	PFHxS	$^{18}O_2$-PFHxS
Perfluorooctane sulfonic acid[a]	8	PFOS	$^{13}C_4$-PFOS
Perfluoroalkyl carboxylic acids (PFCA)			
Perfluorohexanoic acid	5	PFHxA	$^{13}C_2$-PFHxA
Perfluoroheptanoic acid	6	PFHpA	$^{13}C_4$-PFHpA
Perfluorooctanoic acid	7	PFOA	$^{13}C_4$-PFOA
Perfluorononanoic acid	8	PFNA	$^{13}C_5$-PFNA
Perfluorodecanoic acid	9	PFDA	$^{13}C_2$-PFDA
Perfluoroundecanoic acid	10	PFUnDA	$^{13}C_2$-PFUnDA
Perfluorododecanoic acid	11	PFDoDA	$^{13}C_2$-PFDoDA
Perfluorotridecanoic acid	12	PFTriDA	$^{13}C_2$-PFDoDA
Perfluorotetradecanoic acid	13	PFTeDA	$^{13}C_2$-PFDoDA
Perfluoropentadecanoic acid	14	PFPeDA	$^{13}C_2$-PFDoDA

[a]Branched and linear isomers

A procedural blank and QC serum sample was included with every batch of samples. For targets observable in method blanks, MQLs were based on 3× standard deviation of the blanks. For those with no observable blank contamination, MQLs were calculated based on a signal to noise ratio of 3 using the lowest calibration point. Further method validation parameters are provided in Glynn et al. (2012).

Calculations and statistical analyses

When PFAS concentrations were below the MQL, MQL/√2 was taken as an estimated value in the statistical analyses. Multiple linear regressions (MINITAB 15® Statistical Software for Windows) were used to analyze associations between PFAS concentrations in child serum and sampling year. Logarithmically-transformed PFAS concentrations were used, since the distribution of data closely followed a log-normal distribution. Child age, weight and length at sampling were included as covariates in the analyses. In step 1 trends in the whole cohort were analyzed and also for the three age groups 4, 8 and 12 years separately. In step 2, the children were grouped according to where they lived at the time of sampling, using the modelled distribution of PFAS-contaminated drinking water for the period after 2007

(Gyllenhammar et al. 2015). Children were divided into a group including children living in areas not receiving contaminated water and another group of children living in areas receiving <10-60% contaminated water (Figure 1). The aim was to investigate if ingestion of contaminated drinking water affected temporal trends.

As a consequence of the logarithmic transformation, the associations between sampling year and PFAS concentrations are presented as percent change of concentrations per year, and not as change in absolute levels.

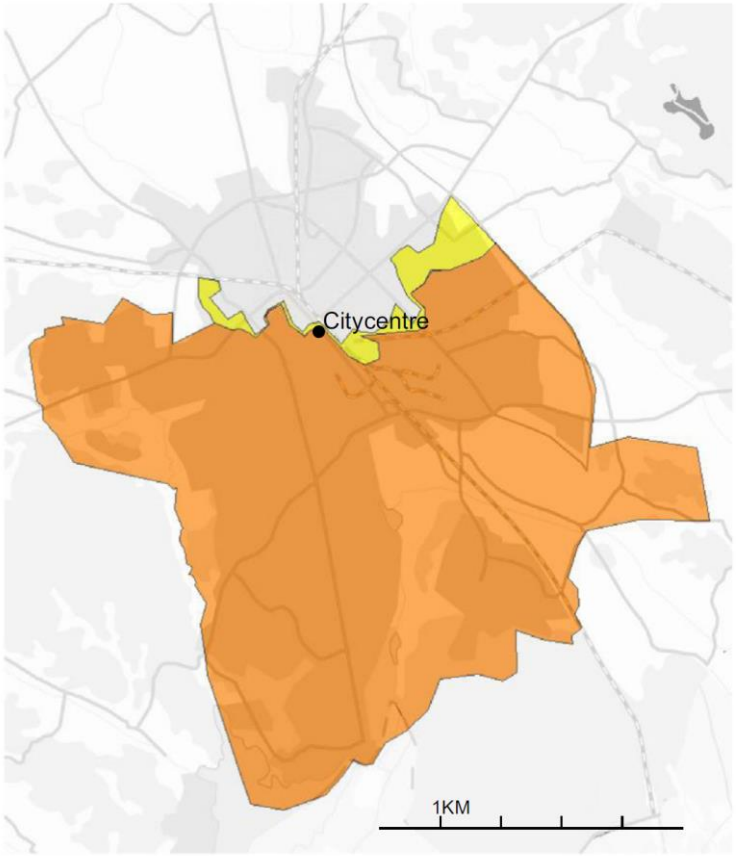

Figure 1. Modelled distribution of PFAS-contaminated drinking water for the period January 2007 to July 2012. No colour: no contaminated water, yellow colour: districts receiving less than 10% of contaminated water, and orange colour: districts receiving 10-60% contaminated water (Gyllenhammar et al. 2015).

Table 3. Concentrations of perfluoroalkyl carboxylic acids (PFCA) (ng/g) in serum samples from children at 4, 8, and 12 years of age from Uppsala, Sweden.

Substance	Age	n	<LOQ (%)	Mean	Median	Range
PFHxA	4	57	98			<LOQ – 0.22
	8	55	100			
	12	119	100			
PFHpA	4	57	21	0.18	0.12	<LOQ – 1.0
	8	55	40	0.12	0.084	<LOQ – 0.75
	12	119	49	0.086	0.058	<LOQ – 0.52
PFOA	4	57	0	2.78	2.52	0.86 – 8.3
	8	55	2	2.13	2.04	<LOQ – 4.0
	12	119	0	2.11	2.04	0.86 – 4.0
PFNA	4	57	0	0.85	0.67	0.26 – 5.5
	8	55	0	0.76	0.69	0.34 – 2.1
	12	119	1	0.67	0.59	<LOQ – 3.9
PFDA	4	57	2	0.26	0.25	<LOQ – 0.54
	8	55	4	0.30	0.29	<LOQ – 0.67
	12	119	1	0.25	0.23	<LOQ – 0.52
PFUnDA	4	57	26	0.21	0.18	<LOQ – 0.77
	8	55	22	0.20	0.18	<LOQ – 0.46
	12	119	35	0.17	0.16	<LOQ – 0.51
PFDoDA	4	57	88			<LOQ – 0.21
	8	55	100			<LOQ
	12	119	99			<LOQ – 0.061
PFTrDA	4	57	65			<LOQ – 0.35
	8	55	49			<LOQ – 0.13
	12	119	71			<LOQ – 0.10
PFTeDA	4	57	89			<LOQ – 0.43
	8	55	100			<LOQ
	12	119	97			<LOQ – 0.094
PFPeDA	4	57	96			<LOQ – 0.058
	8	55	98			<LOQ – 0.042
	12	119	99			<LOQ – 0.015

Results and discussion

PFAA levels in children

Levels of PFHxA, PFDoDA, PFTriDA and PFTeDA and PFPeDA, were generally less than 0.5 ng/ g serum and over 50% of the data were below MQL (Tables 3 and 4). Among perfluoroalkyl carboxylic acids (PFCAs) the median level was highest for PFOA (2.1-2.7 ng/g serum) and declined in the order PFOA>PFNA>PFDA~PFUnDA>PFHpA. Sulfonic acids PFOS and PFHxS had median levels ranging from 1.6 to 5 ng/g, whereas median levels of PFBS were lower than 0.1 ng/g serum (Table 4).

Table 4. Concentrations of perfluoroalkyl sulfonic acids (PFSA) (ng/g) in serum samples from children at 4, 8, and 12 years of age from Uppsala, Sweden.

Substance	Age	n	<LOQ (%)	Mean	Median	Range
PFBS	4	57	35	0.028	0.019	<LOQ – 0.11
	8	55	56			<LOQ – 0.086
	12	119	40	0.027	0.015	<LOQ – 0.23
PFHxS[a]	4	57	0	6.9	5.00	0.60 – 37
	8	55	0	3.9	1.58	0.43 – 30
	12	119	0	3.8	1.64	0.43 – 26
lin-PFOS	4	57	0	2.9	2.40	0.87 – 7.1
	8	55	0	3.8	3.21	1.28 – 19
	12	119	0	3.7	3.35	1.20 – 9.7

[a]Sum of linear and branched isomers

Temporal trends

The temporal trends varied depending on compound and area of residence (Tables 5 and 6). Similar trends were observed among individual PFASs when data from the whole cohort and different age groups were compared (Table 5). Declining trends were observed for PFHpA, PFOA and PFOS, whereas increasing trends were found for PFUnDA. PFNA and PFBS did not show significant trends, whereas the increasing trend of PFHxS and decreasing trend of PFDA was significant only when the whole group was studied (Table 5).

Table 5. Percent change in concentrations of PFAA per year in serum from children in Uppsala 2008-2015, at 4, 8, and 12 years of age. Adjusted for exact age, weight, and length.

Compound	**Age**	**n**	**Change (%)** Mean (SE)	**R^2**	**P**
PFHpA	4	57	- 4.5 (5.4)	8	0.41
	8	**52**	**- 15.9 (5.2)**	**23**	**0.003**
	12	**111**	**- 6.8 (2.7)**	**11**	**0.015**
	All	**218**	**- 7.6 (1.8)**	**20**	**<0.001**
PFOA	4	57	- 4.3 (3.2)	16	0.18
	8	**52**	**- 13.2 (3.1)**	**43**	**<0.001**
	12	**113**	**- 6.0 (2.2)**	**9**	**0.009**
	All	**221**	**- 7.2 (1.3)**	**18**	**<0.001**
PFNA	4	57	5.5 (4.1)	19	0.18
	8	53	0.9 (3.9)	6	0.82
	12	113	- 0.7 (3.3)	5	0.82
	All	223	- 0.5 (1.8)	2	0.77
PFDA	4	57	- 2.4 (3.1)	25	0.45
	8	53	- 4.9 (3.4)	12	0.16
	12	113	- 4.1 (2.7)	4	0.13
	All	**219**	**- 4.1 (1.4)**	**6**	**0.003**
PFUnDA	**4**	**56**	**9.5 (3.6)**	**16**	**0.011**
	8	53	4.0 (3.8)	13	0.30
	12	113	2.2 (2.6)	3	0.40
	All	**222**	**3.4 (1.5)**	**5**	**0.021**
PFBS	4	57	0.4 (7.1)	5	0.95
	8	53	- 3.1 (8.4)	1	0.71
	12	113	2.0 (6.0)	11	0.74
	All	223	0.6 (3.3)	2	0.86
PFHxS[a]	4	57	8.6 (7.6)	6	0.26
	8	53	- 7.9 (9.1)	11	0.38
	12	113	10.9 (6.8)	15	0.11
	All	**223**	**8.1 (3.7)**	**14**	**0.027**
lin-PFOS	4	57	0.2 (3.9)	10	0.97
	8	53	- 8.3 (4.9)	21	0.094
	12	**113**	**- 7.3 (3.1)**	**9**	**0.021**
	All	**222**	**- 5.6 (1.8)**	**10**	**0.001**

[a]Sum of branched and linear isomers

Diverging trends were observed for some PFAS when the children were divided up in two groups; those living in areas with no PFAS-contaminated drinking water and those living in areas that had received contaminated water (Table 6). For PFHpA a relatively rapid decline (12% per year) was observed among children not receiving contaminated water, whereas children receiving contaminated water had stable PFHpA levels during the whole study period (Table 6). PFHxS increased almost 3 times more rapidly in children receiving contaminated water (14% per year) than in children not receiving contaminated water (5% per year). The decline in PFOS levels were slower among children receiving contaminated drinking water than among those not receiving contaminated water. No differences were seen for PFOA, PFNA, PFUnDA and PFBS (Table 6).

Table 6. Percent change in concentrations of PFAAs per year in serum from children in Uppsala 2008-2015, depending on city district receiving PFAS-contaminated water (2 and 3) or not (0 and 1). Adjusted for exact age, weight, and length.

Compound	**City district**	**n**	**Change (%)** Mean (SE)	**R^2**	**P**
PFHpA	0 and 1	**150**	**- 11.9 (2.3)**	**25**	**<0.001**
	2 and 3	70	0.4 (3.2)	23	0.91
PFOA	0 and 1	**151**	**- 7.9 (1.5)**	**20**	**<0.001**
	2 and 3	**70**	**- 6.2 (2.5)**	**16**	**0.014**
PFNA	0 and 1	153	- 1.1 (2.2)	4	0.64
	2 and 3	70	- 0.2 (3.1)	1	0.94
PFDA	0 and 1	**152**	**- 4.9 (1.6)**	**8**	**0.003**
	2 and 3	70	- 1.7 (3.0)	3	0.59
PFUnDA	0 and 1	153	2.8 (1.8)	6	0.13
	2 and 3	70	5.0 (2.9)	7	0.088
PFBS	0 and 1	153	2.0 (2.9)	3	0.48
	2 and 3	70	- 3.4 (6.5)	9	0.61
PFHxS	0 and 1	**152**	**5.3 (2.6)**	**25**	**0.044**
	2 and 3	**70**	**13.6 (5.5)**	**22**	**0.016**
lin-PFOS	0 and 1	**152**	**- 6.5 (2.1)**	**15**	**0.002**
	2 and 3	70	- 2.8 (3.1)	4	0.38

Significant temporal trends were observed although the study period only spanned over 8 years. This suggests that there have been marked changes in exposure of Uppsala children to some of the PFASs during this period. The changes in exposure has, however, not been evenly distributed in the studied group of children. For instance PFHpA declined over 10% per year among children living in areas that had not received PFAS-contaminated drinking water, whereas no change in PFHpA levels was observed among children in the contaminated district. This suggests that the drinking water exposure to PFHpA was high enough to "compensate" for a decline in PHpA exposure from other sources. Such an effect of drinking water exposure, albeit not as drastic, was also observed for PFOS, with a slower decline in the contaminated areas.

The other drinking water-related compounds were PFHxS and PFBS. For PFBS no significant temporal trends were observed, which could be due to levels being low and to a large degree below the MQL. For PFHxS serum levels increased in both study areas, but the increase was much faster in the area receiving contaminated water.

In this study we only had information about the area of residence at the time of sampling. Most probably, some of the children had moved during the period between birth and sampling, which in some cases may have affected the PFAS exposure pattern. With knowledge about places of residence during the whole period and also with knowledge about the location of schools and day-care centres the children have attended, a more detailed picture of changes in exposure patterns could most probably be attained.

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