THE SAHLGRENSKA ACADEMY
INSTITUTE OF MEDICINE

TECHNICAL REPORT

Half-lives of PFOS, PFHxS and PFOA

after end of exposure to contaminated drinking water

Ying Li[1]
Daniel Mucs[2]
Kristin Scott[3]
Christian Lindh[3,4]
Pia Tallving[3]
Tony Fletcher[5]
Kristina Jakobsson[1,3]

[1]Occupational and Environmental Medicine, Gothenburg University
[2]Swetox, Karolinska Insitute, Unit for Toxicological Sciences-Södertälje
[3]Occupational and Environmental Medicine, Lund University
[4]Occupational and Environmental Medicine, Scania Region
[5]London School of Hygiene and Tropical Medicine

REPORT NO 2:2017

FROM THE UNIT FOR OCCUPATIONAL & ENVIRONMENTAL MEDICINE IN GOTHENBURG

In collaboration with:

Table of Contents

Summary

The present knowledge on PFAS elimination in humans after the end of a dominating source of exposure is scarce. For PFOS and PFHxS only data from fluorochemical workers exist, while a few studies in general populations have reported data for PFOA after end of exposure by drinking water. We here report the first results of analyses of half-life for PFOS, PFHxS and PFOA in a Swedish general population with high exposure in drinking water following cessation of exposure, and compare with hitherto unpublished data on PFOS and PFOA elimination from the C8 study in Ohio, USA.

Among 106 persons observed between 6 and 33 months after end of exposure to contaminated drinking water, the shortest half-life was observed for PFOA, mean 2.7 years. The half-life for PFHxS was twice as long, 5.3 years. For PFOS the mean was 3.4 years. The interindividual variation was substantial, with a threefold difference between the 5 and 95 percentiles. In addition, there were also a few extreme outliers. The estimates are well in line with observations in retired fluorocarbon workers, and with observations on PFOA half-live from the C8 study.

Introduction

Perfluorinated and polyfluorinated substances (PFASs) comprise a group of many different synthetic substances that have been produced and widely used for approximately 50 years. They are found in industrial applications and household products mainly due to their properties of withstanding heat, oil, dirt and water. PFASs are also used as surfactants in firefighting foam of the AFFF (Aqeuous Film Forming Foam) type (Thalheimer et al 2017).

In the general population, the dominating sources of exposure are through diet and consumer products (Vestergren and Cousins, 2009; Vestergren et al, 2012). However, during the past decade it has become apparent that localised PFAS contamination to surface and groundwater occurs around military and civilian firefighting training facilities where large quantities of AFFF foams have been used. These substances are further disseminated by means of groundwater flows, and may also reach drinking water wells.

PFASs are excreted via urine and faeces. In observational studies, based on observations in individuals followed over time, half-lives (T½) between 2 to 3 years were reported for PFOA, while longer half-lives for PFOS and PFHxS, 4 and 7 years, respectively (Table 1). Time-trend studies during periods of observed decay reported half-lives in similar ranges, except for PFBS which has a much shorter half-life, 1 month (Olsen et al, 2008). There are no human data after end of exposure for other PFASs.

In animals T½ for PFASs vary markedly between species and are usually much shorter than in humans, with elimination half-life counted in hours or days. Reabsorption by organic anion transporters (OATs) in the kidneys and extensive uptake from enterohepatic circulation for PFOS and PFOA are believed to be more active processes in humans, slowing down the excretion of these substances (Lau et al; 2007). An increased renal elimination at high doses indicates a capacity-limited, saturable renal resorption process via high efficiency OATs (Loccisano et al; 2012; Andersen et al; 2006). Moreover, in a PFOA-exposed US population, the excretion rate was related to polymorphisms (SNPs) in tubular transporter proteins (Fletcher et al; 2012). The faecal elimination is little studied in humans, with the exception of some case reports which indicate that cholestyramine, a lipid lowering pharmaceutical, may enhance elimination (Genuis et al; 2010).

Table 1. Half-lives for PFOS, PFHxS and PFOA in humans

Reference	Setting	Model	Subjects	Initial PFAS level (ng/mL; serum if not specified)	Halflife (years)		
					PFOS	PFHxS	PFOA
Direct observation							
Olsen et al 2007	Retired fluorochemical workers, followed 5 years. Repeated samplings with batch-wise analysis.	First order elimination First and last sample	22 men, 2 women Age 55-75	Median (range) PFOS: 626 (145-3490) PFHxS: 193 (16-1295) PFOA: 408 (72-5100)	Median 4.6, range 2.4-21.7 GM 4.8 95% CI 4.0-5.8	Median 7.1, range 2.2-27.0 GM 7.3 95% CI 5.8-9.2	Median 3.4, range 1.5-9.1 GM 3.5 95% CI 3.0-4.1
Brede el al 2010	Drinking water exposure to PFOA, follow –up 2 years after installation of charcoal filters	First order elimination First and last sample	20 children 20 mothers 20 men	Median (range PFOS: ≈7 (2.6,33.3) PFHxS: ≈1.3(<0.1-13.4) PFOA: ≈25 (6.4-77.5)	-	-	GM 3.26 (range 1.03-14.67)
Bartell et al 2010	Drinking water exposure to PFOA, follow –up after installation of charcoal filter Repeated sampling, follow-up after 1 year	First order elimination Mixed models, 5 samples per person	100 men 100 women Age 53±15	Mean, SD PFOA 180±209	-	-	Median 2,3 95% CI 2.1-2.4
Gomis et al 2016	Ski waxers; followed after marked reduction of occupational exposure		4 men	Range 250-1050	-	-	Median 2.4, range 2.0-2.8
Time trend in populations; selected studies							
Spliethoff et al 2008	Dried blood spots from newborns; 2000-2006	First order elimination	240 samples per year	Whole blood PFOS (0,8-2,4) PFHxS (1.2-2.5) PFOA: (0.3-1.4)	4.1 95% CI 3.1-7.2	8.2 (5.4-16.2)	4.4 95% CI 3.0-7.9
Olsen et al 2012	Blood donors, crossectional sampling, USA 2000, 2006, and 2010		100 samples per year	90,99 percentile PFOS: 70, 157 (GM≈30) PFHxS: 6.3,17 PFOA:9, 19.9 (GM≈5)	4.3	-	-
Yeung et al 2013a,b	Population-based crossectional biomonitoring in two German cities 2000-2009		Students, 10 samples per year and city	PFOS (0,4-116) PFHxS (0.08-5.1) PFOA 6.0 (2.4-10)	Halle: 4.8 Munster:4.3	-	Halle: 8.2 Munster 14.9
Gomis et al 2017	Population-based cross-sectional biomonitoring data from USA (NHANES, 1999-2013) and Australia (2003-2011)	Population-based pharmaco-kinetic modelling	NHANES: 2000 per survey, Australia: 24-84 pools per survey	-	Men: USA 3.8, Australia 4.9 Women: USA 3.3 Australia 5	-	Men: USA 2,4, Australia 2.1 Women: USA 2.1 Australia 1.8

Also, certain pharmaceuticals can block OATs (Inui et al 2000). Females have a slightly shorter PFAS half-life explained by menstrual blood losses, but there may also be other sex-specific elimination mechanisms (Wong et al; 2014). In summary, there is reason to expect that there can be a substantial inter-individual variation in elimination, which also was observed in retired fluorochemical workers (Olsen et al; 2007).

Ronneby – a case study from Sweden

In autumn 2013 a survey of groundwater quality in Blekinge county showed alarmingly high levels of PFASs in ground water from a glaceofluvial water reservoir, the Bredåkra delta, which has a military and civil airfield located in its center (Figure 1). Extended water sampling revealed very high levels of PFASs in outgoing drinking water from Brantafors, one of the two

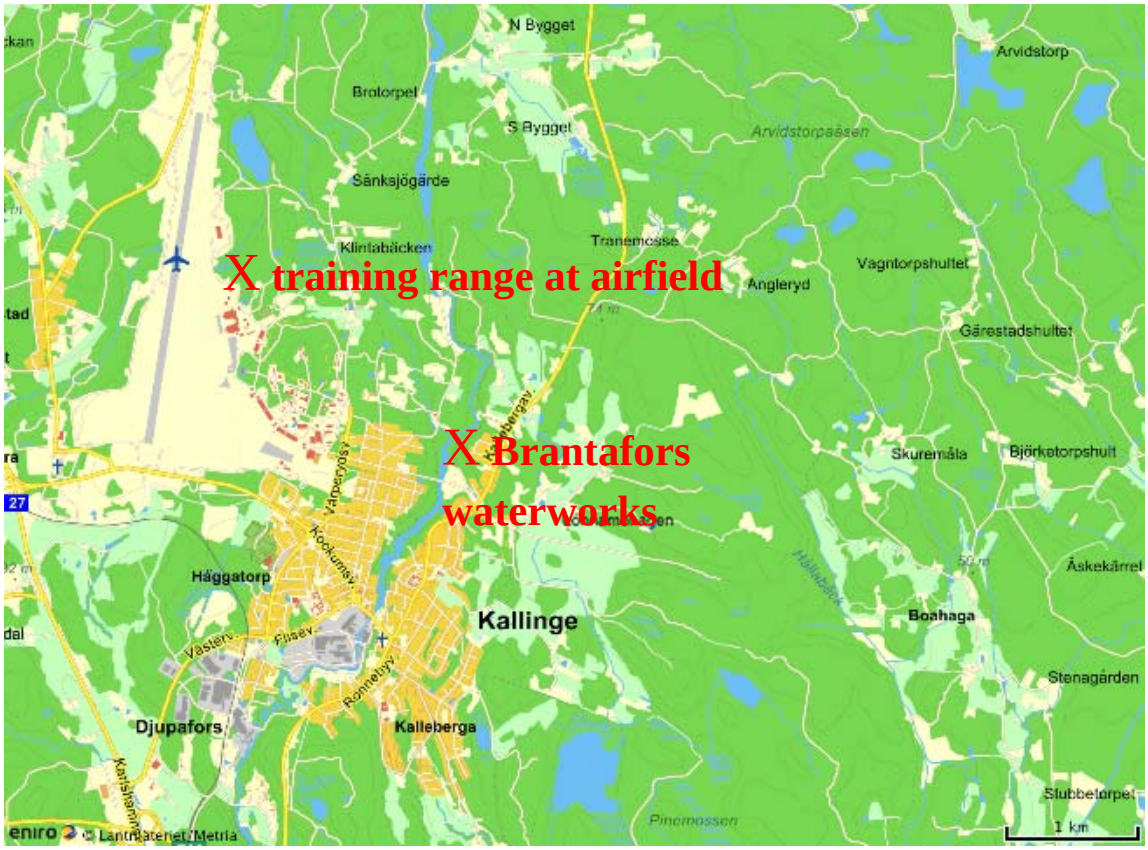


Figure 1. The military and civil air field and the municipal waterworks in Kallinge, Ronneby municipality, Sweden

municipal waterworks in Ronneby municipality (Table 2). This waterworks provided drinking water to 1/3 of the households in Ronneby, a municipality with 28,000 inhabitants. The contaminated waterworks was closed on December 16, 2013, and clean water was promptly provided from Kärragården, the second waterworks in the municipality. After a few days no elevated levels of PFASs could be detected in the distribution network. Brantafors waterworks was reopened in May 2014, supplied with new coal filters and using water only from wells with low PFAs levels, but but the trial was ended in October 2014. During this trial the level of PFASs (sum of 11) were closely monitored, reaching at most 40 ng/L (i.e. well below 90 ng/L, the present Swedish recommended action level).

It was soon confirmed that the fire drill site at the nearby military airport localized within the aquifer area had leached PFASs to the environment. Despite considerable efforts from the

Armed Forces it has not been possible to reconstruct the detailed historical use of AFFF foams at the airfield, but the best estimate as to the start of the use of these foams is the mid 1980s.

Extensive biomonitoring in the municipality population started in June 2014, starting approximately 6 months after end of exposure through drinking water, by open invitations and free of cost. During the period 2014-2016 in total 3418 persons participated. A reference group of 240 subjects from a nearby municipality (Karlshamn) was also examined in 2016.

Table 2. PFASs levels (ng/L) in outgoing drinking water from the waterworks in Ronneby, Sweden on Dec 10, 2013

	Brantafors	Kärragården
Perfluoropentanoic acid, PFPeA	38	10
Perfluorohexanoic acid, PFHxA	320	3.6
Perfluoroheptanoic acid, PFHpA	32	1.4
Perfluorooctanoic acid, PFOA	100	1.0
Perfluorononanoic acid, PFNA	<1	<1
Perfluorodecanoic acid, PFDA	<1	<1
Perfluoroundecanoic acid, PFUnA	<10	<10
Perfluorododecanoic acid, PFDoA	<10	<10
Perfluorobutane sulfonic acid, PFBS	130	<2.6
PErfluorohexane sulfonic acid, PFHxS	1700	4.6
Perfluoroheptane sulfonic acid, PFHpS	60	<1
Perfluorooctane sulfonic acid, PFOS	8000	27

Half-life study

Study group

A panel study group (n=106) with a large age span, 4-83 years, was formed in June 2014. The proportion of females is 53%. The participants have donated blood regularly, initially every third month, then with longer intervals. Analysis of PFASs in serum is performed after each sampling round and the individual results are immediately reported back.

We here report the findings from the first 7 sampling rounds (in June 2014, October 2014, January 2015, April 2015, September 2015, March 2016 and September 2016). The median number of samples per person was 6. Continued sampling twice a year is planned for several years to come.

Chemical analysis

The analyses of PFASs in serum are performed at the department of Occupational and Environmental medicine, Lund University, using LC-MS/MS after precipitation of proteins with organic solvents (Lindh et al; 2012). Isotopically labeled internal standards are used, and the analyses of PFOS and PFOA are part of a quality control program between analytical laboratories coordinated by Professor Hans Drexler, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg, Germany

We here report results from the dominating PFASs in serum: PFOS, PFHxS and PFOA determined as total (not isomer-specific) compounds.

Modelling of half-life

A linear mixed effect model was used to assess subject-specific changes in serum PFAS concentrations over time and to estimate serum elimination half-lives of PFAS. The following mixed model was used to fit the panel data:

$\ln C_{ij} = \alpha_i + t_{ij}k_i + X_i\beta + \varepsilon_{ij}$,

where C_{ij} is the serum PFAS concentrations for individual i and sampling round j, α_i is the subject-specific intercept, t_{ij} is the time elapsed between the clean water was provided and the blood sample collection, k_i is the subject-specific slope, X_i is a vector of fixed covariates for individual i, including age, gender and BMI, β is the fixed effect coefficient and ε_{ij} is the random error term. The subject-specific intercept α_i, the subject-specific slope k_i and the random error term ε_{ij} were modeled as random with normal distribution; others were treated as fixed effects.

The main result for determining half-life is to estimate the mean slope (k_i) and convert that to half-life (ln2/mean(k_i). The values of k_i were predicted using the best linear unbiased prediction (BLUP) method (Robinson 1991). To examine the variability of the half-life the predicted k_i values were converted to half-life, after excluding a small number with negative values (apparently increasing serum PFAS) or extremely high half-life (with minimal k_i).

Summary half live values have been presented as either a mean half life (calculated from the mean elimination rate constant k) or as median half life (the median value of the individually modelled half life values, after excluding a small number of outliers).

Results

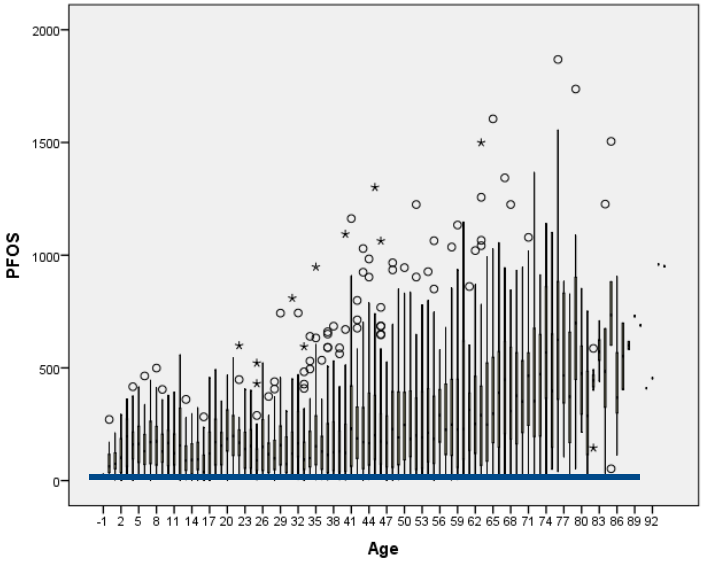
Serum levels at baseline

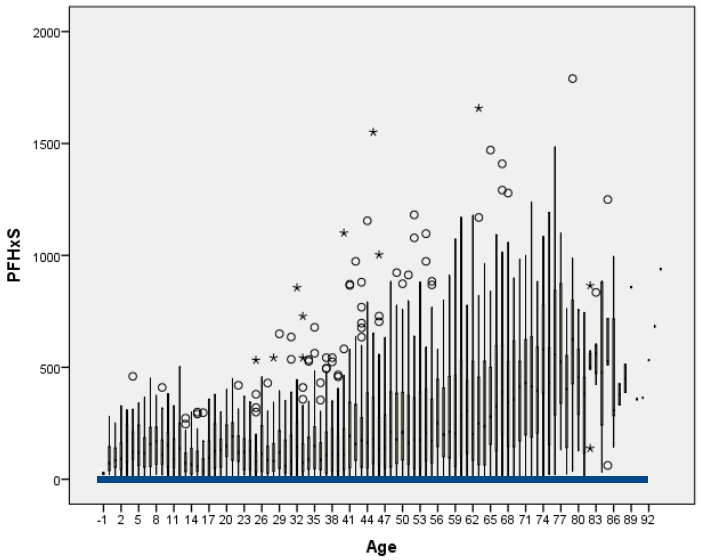
The median serum level of PFHxS was 180 times higher in the investigated Ronneby population compared to the referents from a neighbouring municipality, 42 times higher for PFOS, and 6 times higher for PFOA (Table 3). The distribution of PFAS levels by age is illustrated in Figure 2.

The participants in the panel study initially had serum levels of PFOS, PFHxS and PFOA that were somewhat higher than in the main Ronneby study population. The baseline levels of PFHxS, PFOA and PFOS in the panel study group ranged from 12.3 to 1660 ng/ml, 2.38 to 92 ng/ml and 24.1 to 1500 ng/ml, respectively (Table 3).

Table 3: Summary statistics of PFAS concentrations (ng/ml) in 106 participants in a panel study six months after end of exposure through contaminated drinking water (base-line investigation).

PFAS	Group	No. of participants	mean±sd	[min, median,max]
Serum PFHxS	Panel Study group	106	353±260	[12.3, 277, 1660]
	Main Ronneby group	3418	228±232	[0.14, 152, 1790]
	Reference group	242	1.91±5.27	[0.17, 0.84, 60.1]
Serum PFOA	Panel Study group	106	21.12±14.7	[2.38, 17.5, 92]
	Main Ronneby group	3418	13.7±12.0	[0, 10.4, 91.9]
	Reference group	242	1.77±0.81	[0.22, 1.59, 4.98]
Serum PFOS	Panel Study group	106	387±259	[24.1, 345, 1500]
	Main Ronneby group	3418	245±234	[0.58, 176, 1870]
	Reference group	242	5.68±6.19	[0.27, 4.21, 55.3]





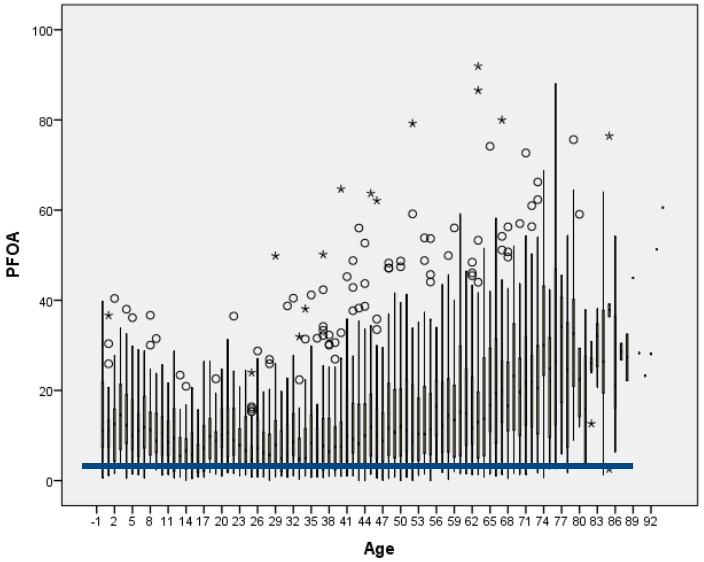


Figure 2: Serum levels of PFOS, PFHxS and PFOA (ng/ml) by age among 3424 persons from Ronneby, participating in open blood samplings 2014-2016.

(Note: scales for y-axis differ)

The horizontal lines represent mean levels among 240 persons from Karlshamn, a nearby municipality in Sweden (PFHxs 1.9 ng/ml, PFOA 1.8 ng/ml, PFOS 5.7 ng/ml).

Decline of serum levels during follow-up

During the follow-up period, from June 2014 to September 2016, the average serum level for PFHxS declined by 25%, PFOA by 28% and PFOS by 35% (Figure 3).

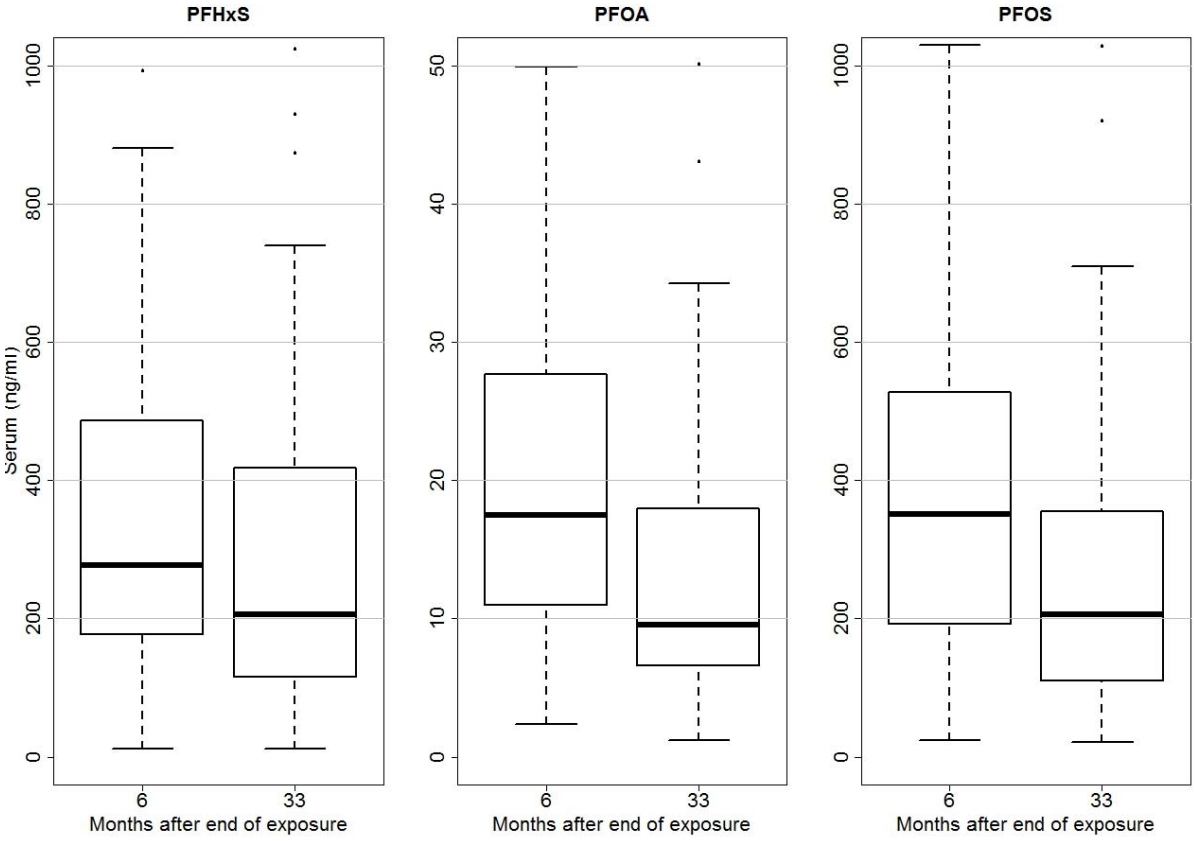


Figure 3: Serum concentrations of PFHxS, PFOA and PFOS in 106 participants in a panel study after end of exposure through contaminated drinking water

Table 4 shows results from the linear mixed effect model and displays the exponentiated parameter estimates. Time after the clean water was provided was associated with a decrease of 0.1309 units in log serum PFHxS per year after adjusting with other covariates, indicating that the average effect of time since clear water was provided was to decrease PFHxS concentration to 88% ($e^{-0.1309}$) of its previous value each year. This elimination rate estimation is equivalent to mean of half-life of 5.29 years (95% CI: 4.72-6.02 years). The average decrease in PFOA was 77% of its previous value each year, corresponding to a mean half-life of 2.67 years (95% CI: 2.47-2.91 years). For PFOS, the annual decrease was to 82%, and the mean half-life 3.40 years (95% CI 3.12-3.74 years). Age at baseline had a strong effect on serum PFHxS, PFOA and PFOS concentrations with average increases of 1.54%, 1.12% and 1.44% per year (see also Figure 2). Gender and BMI were not significantly associated with log-transformed PFAS concentrations.

The distributions of half-lives are shown in Figure 4, after exclusion of outliers for the fitted estimated half-life as follows: those <0 (n=1 for PFHxS) or over 10 years (n=8 for PFHxS, n=1 for PFOS). The median of the half-lives for PFHxS was 5.5 years (5 to 95% range 3.0-9.2 years). For PFOS, the median of half-lives was 3.5 years (5 to 95% range 2.2 to 6.2 years). For PFOA, the median of half-lives for PFOA was 2.7 years (5 to 95% range 1.8 to 5.1 years).

Table 4: Estimated multiplicative effects on serum PFAS concentrations in 106 participants in a panel study after end of exposure through contaminated drinking water.

For PFHxS			
Covariates	Effect multiplier*	P-level	95% CI
Time following clean water provision (per year)	0.8773	<0.0001	0.8635-0.8914
Female	0.9479	0.7117	0.7136-1.2594
Age (per year)	1.0154	<0.0001	1.0081-1.0228
BMI	0.9995	0.9775	0.9643-1.0358
For PFOA			
Covariates	Effect multiplier*	P-level	95% CI
Time following clean water provision (per year)	0.7716	<0.0001	0.7554-0.7883
Female	1.0238	0.8446	0.8090-1.2955
Age (per year)	1.01119	0.0001	1.0058-1.018
BMI	0.9908	0.5418	0.9619-1.0206
For PFOS			
Covariates	Effect multiplier*	P-level	95% CI
Time after the clear water was provided(per year)	0.8156	<0.0001	0.8007- 0.8308
Female	0.9981	0.9881	0.7752-1.2849
Age (per year)	1.0144	<0.0001	1.0079-1.0209
BMI	0.9955	0.7831	0.9644-0.9730

*Effect multiplier are calculated from exponentiated coefficients from a log PFAS linear mixed effect model adjusting for all the covariates listed in the table.

Discussion

Among 106 person observed between 6 and 33 months after end of exposure to PFAS contaminated drinking water the shortest half-life was observed for PFOA, mean 2.67 years. The half-life for PFHxS was twice as long, 5.29 years. For PFOS the mean was 3.40 years.
This pattern is similar to observations in 24 retired fluorocarbon workers, to our knowledge the only other study that hitherto has reported half-lives for PFOS and PFHxS after end of exposure that is substantially higher than the general population background (Olsen et al, 2007). The retired workers were older than our population, had higher serum levels of PFOA and PFOS, and were followed for a longer period, 5 years.

Our estimate of half-life for PFOA was similar to that reported from populations living in PFOA-polluted areas around production plants, followed for 1-2 years after provision of clean drinking water (Brede et al, 2010; Bartell et al, 2010).

For comparison (see data in Appendix), the estimated half-life for both PFOS and PFOA, based on hitherto unpublished data from a 4 year follow-up in the C8 study population, and calculated with the same method as for the Ronneby population, were similar. Within C8 the mean half-life for PFOA was 2.72 years, very close to the results in Ronneby, and for PFOS the half-life was 3.60 years, slightly longer. It should be noted that the C8 population had serum PFOA levels that were substantially higher than the Ronneby population. In contrast, PFOS levels were much lower in the C8 population, with little direct exposure from drinking water. For PFOS, the population half-life has been estimated to be 4.3 years from studies in US blood

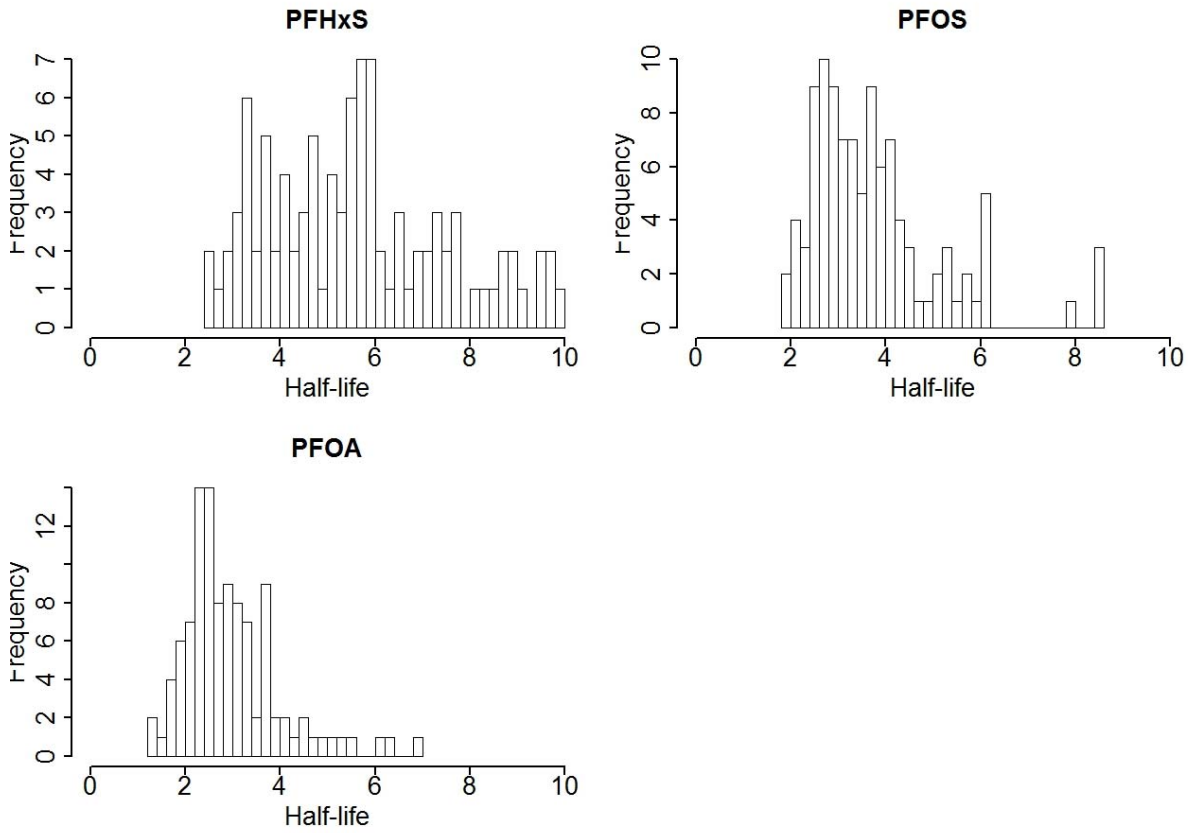


Figure 4: The interindividual variation of half-lives for PFAS in 106 participants in a panel study after end of exposure through contaminated drinking water, excluding outliers.

donors (Olsen et al, 2012). After an abrupt end of a dominating source of exposure, as in Ronneby, the finding of a shorter half-life is as expected.

In both the Ronneby the inter-individual variation in half-lives was substantial, with a 3-fold difference between the 5 and 95 percentiles, and with a few extreme outliers with extremely long half-lives. Large inter-individual differences were also observed in the C8 population and in the retired fluorocarbon workers (Olsen et al, 2007). Another next step in our study of PFAS elimination will be to explore the determinants for such differences.

In addition to differences between individuals as to excretion capacity, recent data using paired human serum and urine samples for estimation of T½ have indicated marked differences between excretion of PFASs with different chain-length and isomers (Zhang et al, 2013). It is likely that linear isomers are preferentially retained (Miralles-Marco et al; 2015), but observational longitudinal human data on the excretion of linear versus branched chain isomers is absent. Thus, variation of T½ between populations and between individuals using total PFOS, PFOA and PFHxS determinations (as in this study) may in part reflect body burdens with different isomer composition.

Such differences are likely to be found in humans, given the varying production methods of PFAS over time. Synthesis of PFAS is by electrochemical fluorination or fluorotelomerization. Electrochemical fluorination was used from the 1950s until the early 2000s and yielded branched and linear isomers. By contrast, fluorotelomerization which was later introduced

produces almost exclusively linear compounds (Vyas et al; 2007). The firefighting foams used over time have differed in composition, but there may also be varying fate of different PFAS structural isomers during soil and ground water transportation. Thus, it is of importance to include determination of both linear and branched isomers of PFOS, PFHxS, PFOA in order to understand differences in half-lives.

Follow up of the Ronneby population provides the first time that the excretion half-life can be estimated in a community population with past heavy contamination with PFHxS, whose exposure has been stopped. The mean half-life was 5.27 years though with wide variability between individuals. It would be desirable to understand the causes of such variations. The estimated half-life for PFOA and PFOS of 2.7 and 3.4 years respectively were consistent with results from other studies. They also show wide variability, which needs more research to understand mechanisms.

Limitation

A major limitation of the present preliminary analysis as well as the C8 four year follow-up is that the serum samples were not analyzed in the same batch. All Ronneby samples were analyzed at the same laboratory with the same methods and work-up procedure, but there is still a need for a batched reanalysis of all samples to reduce laboratory variation. This is planned as a next step in our studies.

Acknowledgement

We acknowledge the work of the field team during serum samplings, and the study participants. The study was funded by FORMAS, FORTE and Arbets-och miljömedicin Syd.

Appendix – the C8 study

For comparison with Ronneby, new half-life estimates computed for both PFOA and PFOS are presented from the C8 study population. We here present data here for a larger group than previously published, with longer follow- up and data for PFOS for the first time.

Study group

In the C8 study population of the Mid-Ohio Valley, USA, some 67,000 people provided blood samples in a survey during 2005-6 of those who had lived for at least a year in the water supply district areas contaminated with PFOA from the local plant (Frisbee et al, 2009). Within that cohort, a half-life study was carried out in nearly 200 people. For PFOA the mean half-life was 2.3 years, derived from repeated measurements during the first year since public water filtration was introduced (Bartell et al, 2010). Here we report findings from a larger group of over 700 people who were invited to provide a second sample more than 4 years following the main survey. The first survey took place during 2005-2006, the second during 2010 (Fitz-Simon et al, 2013). The eligible population for recall was aged 20-60 at the time of the first survey, lived within approximately 40km of the blood collection clinic, had consented to be contacted and could be reach by telephone. People with prior cancer diagnoses and reporting active infection were excluded. Within this eligible population, people were randomly selected until the target numbers were reached.

755 individuals were successfully recruited and provided blood samples for analysis, in early 2010, with a further subgroup of 411 supplying a subsequent second sample. The first survey was between Aug 2005 and July 2006, the second between Mar 2010 and Sept 2010, the third survey was during October 2010. The mean time between the first and second survey was 4.4 years, and from first to third survey 4.8 years.

PFASs were assayed in serum samples by accredited labs and serum concentration of PFOA and PFOS were above the detection limit in all participants (Frisbee et al, 2009; Fitz-Simon et al, 2013). Serum concentrations were thus available for two time points in 755 individuals and three time points for 411. Some data were missing (eg for BMI) and in the final models 743 participants contributed at least 2 measurements for the modelling of excretion.

Most (724) of this study population were exposed through their domestic water supplies from one of four of the water supply districts with PFOA contamination. These water supplies received treatment technology to remove PFOA at various dates as follows: March 2006 for Belpre, May 2006 for Tuppers Plain, June 2007 for Lubeck and November 2007 for Little Hocking (Fitz-Simon et al, 2013). Residents in the Little Hocking water district had received large supplies of bottled water prior to filtration and were advised not to consume tap water, and as a consequence their date of stopping intake was uncertain. Therefore, for the analysis of PFOA excretion and half-life, the study population was restricted to individuals resident in the other three districts (Belpre, Lubeck and Tuppers Plain water districts), and the date of stopping intake was taken to be the date of first blood sample or the date of filtration being introduced, whichever was later. The serum level measured at first round was applied at that date. 445 individuals were followed up in those three districts for PFOA excretion. On average, the time for this population from drinking water filtration being supplied to the last blood sample taken was 3.9 years.

PFOS contamination was not related to a local source but national restrictions of use of PFOS in products had dramatically reduced primary exposure to PFOS (Gomis et al, 2017). Thus the population's excretion greatly exceeded its intake and the half-life can be estimated by follow-up from the first sample for all 745 individuals. However the PFOS intake during follow up, while much reduced would not have been zero, given the persistence and with some presumed ongoing exposure to PFOS, the estimated half would overestimated, but this is considered to be only a small degree. PFHxS and PFNA were also measured in the repeat samples, but neither had been subject to regulatory restrictions as PFOS, and serum levels hardly changed over the 4 years and thus these data are uninformative for estimating half-lives for these compounds.

Chemical analysis

At baseline, concentrations were determined using protein precipitation followed by reversed-phase high-performance liquid chromatography/tandem mass spectrometry (Frisbee et al, 2009). At follow-up, the approach followed an online solid phase extraction coupled with reversed-phase high-performance liquid chromatography separation and detection by isotope-dilution tandem mass spectrometry (Kato et al, 2011a). The two techniques are known to produce equivalent results for the analysis of serum PFAAs (Keller et al, 2010). Furthermore, both laboratories participated in an interlaboratory study that reported a reasonable agreement, particularly for PFOS and PFOA (Van Leeuwen et al, 2006).

Modelling of half-lives

A linear mixed effect model was used to assess subject-specific changes in serum PFAS concentrations over time and to estimate serum elimination half-lives of PFAS. The following mixed model was used to fit the panel data:

$$\ln C_{ij} = \alpha_i + t_{ij} k_i + X_i \beta + \varepsilon_{ij} ,$$

where C_{ij} is the serum PFAS concentrations for individual i and sampling round j, α_i is the subject-specific intercept, t_{ij} is the time elapsed between the clean water was provided and the blood sample collection, k_i is the subject-specific slope, X_i is a vector of fixed covariates for individual i, specifically age, gender and BMI, β is the fixed effect coefficient and ε_{ij} is the random error term. The subject-specific intercept α_i, the subject-specific slope k_i and the random error term ε_{ij} were modeled as random with normal distribution; others were treated as fixed effects.

The main result for determining half-life is to estimate the mean slope (k_i) and convert that to half-life (ln2/mean(k_i). The values of k_i were predicted using the best linear unbiased prediction (BLUP) method (Robinson, 1991). To examine the variability of the half-life the predicted k_i values were converted to half-life, after excluding a small number with negative values (apparently increasing serum PFAS) or extremely high half-life (with minimal k_i)

Results

Serum levels of PFOA and PFOS at the first and second survey are reported in Table 1. PFOA dominates, while PFOS levels are in range that can be observed in a US general population (Kato et al, 2011b).

Table 2 shows results from the linear mixed effect model and displays the exponentiated parameter estimates. The average effect of time since clean water was provided was to decrease

PFOA concentration to 82% of its previous value each year. This elimination rate estimation is equivalent to a mean of half-life of 2.72 years (95% CI 2.52 – 2.90). The average effects of time to decrease PFOS was 82% of its previous value each year, corresponding to a mean half-life of 3.60 years (95% CI 3.45 – 3.76). Females had significantly lower PFAS levels. Little effect of BMI fitted as a continuous variable.

Table 1: Descriptive statistics of PFOA and PFOS concentration at base-line and follow-up in individuals from the C8 study. PFOS all water districts, PFOA 3 water districts (see methods).

		No. of individuals	Mean	Sd	min	median	max
PFOA	Survey 1	455	75.5	154.6	1.00	49.1	2495.3
	Survey 2	455	41.5	138.2	0.25	18.5	2140.0
PFOS	Survey 1	755	23.2	14.4	0.25	20.3	93.3
	Survey 2	755	10.9	7.49	0.10	9.20	61.0

Table 2: Estimated multiplicative effects on serum PFAS concentrations in individuals from the C8 study

For PFOS in C8 population n=743			
Covariates	Effect multiplier*	P-level	95% CI
Time during follow up 2005-10 (per year)	0.8248	<0.0001	0.8179-0.8318
Female	0.7162	<0.0001	0.6480-0.7916
Age (per year)	1.0064	0.0048	1.0020-1.0109
BMI	0.9934	0.0813	0.9859-1.0008

For PFOA in C8 population of 3 water districts n=437			
Covariates	Effect multiplier*	P-level	95% CI
Time since the clean water was provided (per year)	0.7750	<0.0001	0.7594-0.7873
Female	0.9199	0.3915	0.7594-1.1143
Age (per year)	1.0196	<0.0001	1.0109-1.0284
BMI	0.9880	0.096	0.9741-1.0022

After excluding some outliers for the fitted estimated half-life (<0 (for PFOA n=9 and for PFOS n=6) or over 10 years (for PFOA n= 15 and for PFOS n=10)), the distribution of half-life is illustrated in *Figure 1*, with median values of 2.76 years for PFOA (5 to 95% range 1.44-5.82 years)., and 3.72 years for PFOS (5 to 95% range 2.39-5.98 years).

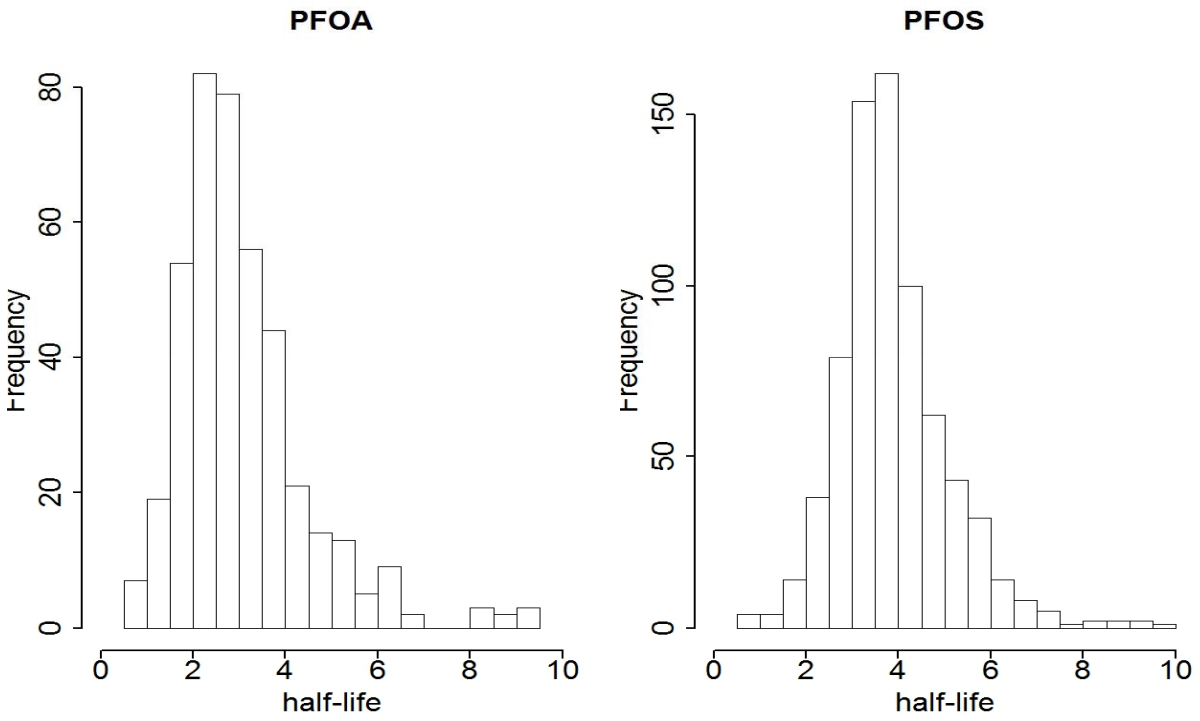


Figure 1. The distribution of half-lives for PFOA in 437 individuals and PFOS in 727 individuals from the C8 study.

Discussion

For PFOA, modelling of serum measurements of 437 individuals with an average of 3.9 years follow-up from provision of clean water in 3 water districts to the last measurement, resulted in an estimated average half-life of 2.72 years (95% CI 2.52 – 2.90). This is a little longer than the half-life of 2.3 years in the first year already reported (Bartell et al, 2010), however the populations are not entirely comparable. The population in the Bartell study was more weighted to individuals with higher initial PFOA levels and they note that the Little Hocking subpopulation (which was excluded from our analysis due to uncertainty in the date of stopping PFOA intake) were most exposed and showed a shorter half-life, suggesting results more consistent with the current findings for the remaining population. The main limitations of the current study was that we could not take into account the role of reported bottled water usage, and that our model assumes that first measured serum sample was representative of the serum at the date of water filtration that may have been several months later. A further limitation is that analyses were done by different laboratories at different times.

For PFOS, modelling of serum measurements of 743 individuals with an average of 4.8 years follow-up from first serum sample to the last measurement, resulted in an estimated average half-life of 3.60 years (95% CI 3.45 – 3.76). To be a true indicator of half-life during this observation period, then intake must have stopped completely. This is unlikely to be the case, thus the fall would be slower and the true half-life would be overestimated. However the rate of fall in PFOS intake is estimated to be steep (Gomis et al, 2017) and thus this bias is expected to be quite small.

References

Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect. 2010 Feb;118(2):222-8.

Brede E, Wilhelm M, Göen T, Müller J, Rauchfuss K, Kraft M, Hölzer J. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int J Hyg Environ Health. 2010 Jun;213(3):217-23.

Fitz-Simon N, Fletcher T, Luster MI, Steenland K, Calafat AM, Kato K, Armstrong B. Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid. Epidemiology. 2013 Jul;24(4):569-76.

Fletcher, Tony ; Yucesoy, Berran ; Bartell, Scott ; Mondal, Debapriya ; Fitz-Simon, Nicola ; Luster, Michael. Genetic variation in kidney transporter proteins and serum half-lives of perfluoroactanoic acid (PFOA) and perfluoroactane sulfonic acid (PFOS). Epidemiology, 2012, Vol.23, p.1

Frisbee SJ, Brooks AP Jr, Maher A, et al. The C8 health project: design, methods, and participants. Environ Health Perspect. 2009;117: 1873–1882.

Genuis SJ, Birkholtz D, Ralitsch M et al. Human detoxification of perfluorinated compounds. Public Health 2010;124(7) 367-75.

Gomis MI, Vestergren R, Nilsson H, Cousins IT. Contribution of Direct and Indirect Exposure to Human Serum Concentrations of Perfluorooctanoic Acid in an Occupationally Exposed Group of Ski Waxers. Environ Sci Technol. 2016 Jul 5;50(13):7037-46.

Gomis MI, Vestergren R, MacLeod M, Mueller JF, Cousins IT. Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. In Gomis MI: From emission sources to human tissues: modelling the exposure to per-and polyfluoroalkyl substances. PhD Thesis, Stockholm University, 2017.

Hölzer J, Göen T, Rauchfuss K, Kraft M, Angerer J, Kleeschulte P, Wilhelm M. One-year follow-up of perfluorinated compounds in plasma of German residents from Arnsberg formerly exposed to PFOA-contaminated drinking water. Int J Hyg Environ Health. 2009 Sep;212(5):499-504.

Inui K-I, Masuda S, Saito H. Cellular and molecular aspects of drug transport in the kidney. Kidn Internat 2000;58:944-58.

Kato K, Basden BJ, Needham LL, Calafat AM. Improved selectivity for the analysis of maternal serum and cord serum for polyfluoroalkyl chemi- cals. J Chromatogr A. 2011a;1218:2133–2137.

Kato K, Wong LY, Jia LT, Kuklenyik Z, Calafat AM. Trends in exposure to polyfluoroalkyl chemicals in the U.S. Population: 1999-2008. Environ Sci Technol. 2011b;45:8037–8045.

Keller JM, Calafat AM, Kato K, et al. Determination of perfluorinated alkyl acid concentrations in human serum and milk standard reference materials. Anal Bioanal Chem. 2010;397:439–451.

Loccisano AE, Campbell JL Jr, Andersen ME, Clewell HJ 3rd. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. Regul Toxicol Pharmacol. 2011 Feb;59(1):157-75.

Miralles-Marco A et al. Perfluorooctane sulfonate: A review of human exposure, biomonitoring and the environmental forensics utility of its chirality and isomer distribution. Environ Int 2015;77:148-59

Nilsson H, Kärrman A, Westberg H, Rotander A, van Bavel B, Lindström G. A time trend study of significantly elevated perfluorocarboxylate levels in humans after using fluorinated ski wax. Environ Sci Technol. 2010 Mar 15;44(6):2150-5.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect. 2007 Sep;115(9):1298-305.

Olsen GW, Mair DC, Church TR, Ellefson ME, Reagen WK, Boyd TM, Herron RM, Medhdizadehkashi Z, Nobiletti JB, Rios JA, Butenhoff JL, Zobel LR. Decline in perfluorooctanesulfonate and other polyfluoroalkyl chemicals in American Red Cross adult blood donors, 2000-2006. Environ Sci Technol. 2008 Jul 1;42(13):4989-95.

Olsen GW, Chang SC, Noker PE, Gorman GS, Ehresman DJ, Lieder PH, Butenhoff JL. A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans. Toxicology. 2009 Feb 4;256(1-2):65-74.

Olsen GW, Lange CC, Ellefson ME, Mair DC, Church TR, Goldberg CL, Herron RM, Medhdizadehkashi Z, Nobiletti JB, Rios JA, Reagen WK, Zobel LR. Temporal trends of perfluoroalkyl concentrations in American Red Cross adult blood donors, 2000-2010. Environ Sci Technol. 2012 Jun 5;46(11):6330-8.

Robinson G. That BLUP is a Good Thing: The Estimation of Random Effects. Statistical Science,1991;6(1), 15-32.

Seals R, Bartell SM, Steenland K. Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. Environ Health Perspect. 2011 Jan;119(1):119-24.

Thalheimer AH, McConney LB, Kalinovich IK, Pigott AV, Franz JD, Taylor Holbert H, Merical D, Puchacz ZJ. Use and potential impacts of AFFF containing PFASs at airports. National Academies of Sciences, Engineering, and Medicine. ISBN 978-0-309-44638-9.

Van Leeuwen SJP, Kärrman A, Van Bavel B, De Boer J, Lindström G. Struggle for quality of determination of perfluorinated contaminants in human and environmental samples. Environ Sci Technol. 2006;40: 7854–7860.

Vyas SM. Differences in the isomer composition of perfluoroctanesulfonyl (PFOS) derivatives. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2007 Feb 15;42(3):249-55.

Wong F, MacLeod M, Mueller JF, Cousins IT. Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: evidence from population-based pharmacokinetic modeling. Environ Sci Technol. 2014;48(15):8807-14.

Zhang Y, Beesoon S, Zhu L, Martin JW. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol. 2013 Sep 17;47(18):10619-27.

Zhang Y et al. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol. 2013 Sep 17;47(18):10619

THE LATEST PUBLISHED REPORTS

from the Unit for Occupational & Environmental Medicine in Gothenburg

Report 2017:1
Airdrome Aviation Safety Climate Questionnaire (ADASCQ). Utveckling av enkätinstrument för att mäta organisations-klimat för hög flygsäkerhet vid flygplats-arbete.

Authors: Törner M, Pousette A, Vega-Matuszczyk J, Björk K

Report 2015:1
Hälsa och framgång! Organisationsklimat för hälsa, säkerhet, innovation och effektivitet. Slutrapport. Sahlgrenska akademin, Göteborgs universitet.

Authors: Törner M, Pousette A, Larsman P, Eklöf M, Hemlin S.

Report 2014:2
Jämförelse av fysiologisk respons vid exponering för buller eller vibrationer

Authors: Michael Smith, Mikael Ögren, Kersin Persson Waye

Report 2014:1
Sammanfattningar av projektarbeten. Behörighetsutbildning i försäkringsmedicin 2013

Authors: Students (See GUPEA and the full text PDF)

Report 2013:2
Olägenheter till följd av petrokemisk industri i Stenungsund 2012

Authors: Anita Gidlöf-Gunnarsson, Lars Barregård

Report 2013:1
Säkerhetsklimat i vård och omsorg. Bakomliggande faktorer och betydelse för personalsäkerhet och patientsäkerhet

Authors: Marianne Törner, Mats Eklöf, Pernilla Larsman, Anders Pousette

Report 2011:8
Akustikförsök - Forskarfredag 2010

Author: Kerstin Persson Waye

Report 2011:7
God ljudmiljö i skola - beskrivning av rumsakustik före och efter åtgärdsprogram

Author: Pontus Larsson

Report 2011:6
God ljudmiljö i förskola - beskrivning av rumsakustik före och efter åtgärdsprogram

Author: Pontus Larsson

Report 2011:5
Högre säkerhet i livsmedelsindustrin. Ett interventionsprojekt för bättre säkerhetsklimat

Authors: Marianne Törner, Mats Eklöf, Anders Pousette, Christina Stave

Report 2011:4
God ljudmiljö i förskola och skola - krav på rum, bygg - och inredningsprodukter för minskat buller

Authors: Kerstin Persson Waye, Agneta Agge, Marie Hult, Pontus Larsson

Report 2011:3
God ljudmiljö i skola - samband mellan ljudmiljö, hälsa och välbefinnande före och efter åtgärdsprogram

Authors: Kerstin Persson Waye, Agneta Agge, Marie Hult, Pontus Larsson

Report 2011:2
God ljudmiljö i förskola - samband mellan ljudmiljö, hälsa och välbefinnandeföre och efter åtgärdsprogram

Authors: Kerstin Persson Waye, Agneta Agge, Marie Hult, Pontus Larsson

Report 2011:1
Slutrapport Forskningsprogrammet TVANE: Effekter av buller och vibrationer från tåg- och vägtrafik - tågbonus, skillnader och samverkan mellan tåg- och vägtrafik

Authors: Evy Öhrström, Anita Gidlöf-Gunnarsson, Mikael Ögren, Tomas Jerson

The first report was published in 2010.

Published by
the Unit for Occupational & Environmental Medicine
Gothenburg, (2017-05-31)
ISBN 978-91-86863-12-8

This technical report is also published as Report No. 11/2017 by
Occupational and Environmental Medicine at Lund University.

amm@amm.gu.se
031-786 6300
GU rapporter, Box 414, SE-405 30 Gothenburg, SWEDEN

Site: www.amm.se
gupea.ub.gu.se/handle/2077/34412