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Blood serum concentrations of perfluorinated compounds in men from Greenlandic Inuit and European populations

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Abstract

Perfluorinated compound (PFCs), such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), are used in large quantities. They are persistent and found in measurable levels in human serum around the world. They have been associated with developmental, hepatic, and carcinogenic effects in animal studies. The aim of the present study was to describe levels of PFCs in serum among Inuits from Greenland and inhabitants from Warsaw, Poland and Kharkiv, Ukraine. Furthermore, the aim was to define social- and lifestyle related determinants of exposure for these compounds. Serum levels of seven PFCs were analysed by liquid chromatography-tandem mass spectrometry (LC/MS/MS). The concentrations of PFOS and PFOA were the highest of all PFCs in all three populations with a total amount of almost 90% of the PFCs. The mean levels of PFOS and PFOA were in the Greenlandic Inuits 52 and 4.8 ng mL⁻¹, in Poland 19 and 5.2 ng mL⁻¹, and in Ukraine 8.1 and 1.9 ng mL⁻¹, respectively. Thus, levels of PFCs in the serum of Inuits on Greenland were among the highest described in a general population whereas the levels in Poland were similar to other industrialized countries. The exposure in Ukraine was rather low. In the Greenlandic Inuit population, intake of seafood, tea, age and area of living were significant determinants of PFOS concentrations and explained about 22% of the variation. For the other populations no strong determinants were found.

1. Introduction

Perfluorinated compounds (PFCs), such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), have since the 1950's been used in large quantities in a number of applications such as in surface coatings, making products water- and oil resistant, and fire fighting foams. In addition, several of the compounds are approved for use in food containers and cooking pans (e.g. Teflon®) and may thus be transferred to food (Fromme et al., 2009). The annual production of PFCs is in the range of several hundred metric tons per year (Lau et al., 2004).

The use of PFOS and PFOA has decreased in the last years and as a result, levels in human matrices are declining (Harada et al., 2004; Olsen et al., 2005; Calafat et al., 2007; Harada et al., 2007; Jin et al 2007; Olsen et al., 2007; Olsen et al., 2008; Haug et al., 2009; Wilhelm et al., 2009; Sundström et al., 2011; Axmon et al., in manuscript). However, PFOS and PFOA have been substituted by other PFCs, such as perfluorononanic acid (PFNA), perfluorodecanic acid (PFDA) and perfluoroundecanoic acid (PFUnDA). Consequently, human levels of the latter compounds have been found to be increasing (Calafat et al., 2007; Haug et al., 2009; Axmon et al., in manuscript)

In animal studies, PFCs have been found to be associated with several outcomes, such as cancer, neurobehavior and reproductive health problems (Luebker et al., 2005; Jensen and Leffers 2008, Lau et al., 2007; Chang et al., 2008; Johansson et al., 2008; DeWitt et al., 2009, Sonne 2010). Furthermore, the evidence of effects on humans in the general population is increasing. *In utero* exposure to PFOS and PFOA has been suggested to decrease birth weight (Apelberg et al., 2007; Fei et al., 2007; Stein et al., 2009; Washino et al., 2009) as well as weight in early childhood (Andersen et al., 2010). Moreover, associations have been found between body levels of PFCs and sperm count (Joensen et al., 2009), glucose homeostasis and

metabolic syndrome (Lin et al., 2009), attention deficit/hyperactivity disorder (ADHD) (Hoffman et al., 2010) and thyroid function (Dallaire et al., 2009a).

The PFCs are biopersistent compounds with half-lives in humans that have been estimated to be between three and nine years (Olsen et al., 2007; Olsen et al., 2008; Bartell et al., 2010; Brede et al., 2010; Nilsson et al., 2010; Seals et al., 2011). Thus, they will accumulate in humans. In recent years there have been many publications describing serum levels in different populations worldwide (Kannan et al., 2004; Kuklennyik et al., 2004; Guruge et al., 2005; Falandysz et al., 2006; Kärman et al., 2006; Calafat et al., 2007; Fromme et al., 2007; Kärman et al., 2007; Weihe et al., 2008; Harada et al., 2009; Rylander et al., 2009a; Rylander et al., 2009b; Harada et al., 2010; Ingelido et al., 2010; Roosens et al., 2010; Hanssen et al., 2010; Hemat et al., 2010; Vassiliadou et al., 2010; Zhang et al., 2010). Generally, levels in industrialized countries are higher (10-30 ng PFOS mL⁻¹) than in developing countries (few ng PFOS mL⁻¹), although levels in the general population seem to be much lower than those of occupational exposed workers (µg PFOS/mL) (Fromme et al., 2009). However, measurements in many populations are still missing or insufficient. One such population is the Greenlandic Inuits where only recently levels in breast cancer cases and controls have been described (Bonfält-Jørgensen et al., 2011). The levels in the controls were similar to those found in other industrialized countries. This is in accordance with results from Canadian Inuits (Dallaire et al., 2009b; Château-Dégat et al., 2010). However, the levels may be expected to be high in certain areas of Greenland with high intake of local animals, as animals living in polar areas have elevated levels of PFC (Jensen and Leffers 2008).

There is some information about determinants of PFCs in human samples. Diet has been found to be a major determinant (Fromme et al., 2009; Vestergren and Cousins 2009; Egeghy and Lorber 2011; Haug et al., 2011). Among foods suggested to account for this is seafood (Falandysz et al., 2006; Dallaire et al., 2009b; Rylander et al., 2009a; Haug et al., 2010a), meat

(Halldorsson et al., 2008; Haug et al., 2010a), poultry, frozen entrées, fast food, and microwave popcorn (Tittlemier et al., 2007) and peppers, cakes and cookies, lunchmeats, and green vegetables (Ostertag et al., 2009). While food seems to be the most important source of exposure in the general population, some studies have indicated a substantial contribution also from dust and air (Fromme et al., 2009; Gewurtz et al., 2009; Harrad et al., 2010; Egeghy and Lorber 2011; Haug et al., 2011).

Even though some exposure routes for PFCs are well known, this only explains a small proportion of the differences in the human PFC levels. Studies on possible determinants such as age (Harada et al., 2004; Kannan et al., 2004; Calafat et al., 2006; Fromme et al., 2007; Jin et al., 2007; Olsen et al., 2008; Rylander et al., 2009; Wilhelm et al., 2009; Haug et al., 2010a) and gender (Fromme et al., 2009) have so far been inconclusive. Thus, further studies are needed.

In this study, we report serum levels of seven PFCs from Inuit men on Greenland and male inhabitants from Warsaw, Poland and Kharkiv, Ukraine. Furthermore, we investigate determinants of exposure to these PFCs. Such knowledge is important e.g. for risk evaluations and measures for decreasing exposure. The large variation in PFC levels between the different populations may constitute a valuable basis for studies of dose-response studies of different health effects.

2. Materials and methods

2.1. Subjects and data collection

The study population has been described in detail previously (Jönsson et al., 2005). In this study, male subjects delivering semen samples from Greenland, Poland and Ukraine were

investigated. Serum samples were obtained from 196 Greenlandic Inuit males, 190 men from Poland and 203 men from Ukraine in the years 2002-03. Demographic data are shown in Table 1. The study was approved by the local ethical committees representing all participating populations and all subjects signed an informed consent.

2.2. Interview data

Information on lifestyle, medical and reproductive history was collected through interviews. In the present study we used information on age, height and weight (for calculation of BMI), smoking habits, intake of seafood and tea consumption at baseline. For the population from Greenland we also used information regarding area of living, due to different life-styles between different areas, exemplified by different nutrition habits, which might affect PFC levels.

2.3. Collection of blood samples

Blood samples were drawn from a cubital vein into 10 mL vacuum tubes for serum collection without additives (Becton Dickinson, Maylan, France). After cooling to room temperature the tubes were centrifuged at 4000 g for 15 min. Serum was transferred with ethanol rinsed Pasteur pipettes to ethanol rinsed brown glass bottles (Termometerfabriken, Gothenburgh, Sweden). A piece of aluminum foil was placed on top of the bottles which were then sealed. Sera were stored at $-20\text{ }^{\circ}\text{C}$ until shipment, but refrigeration was accepted for up to four days. After the arrival at the analyzing laboratory the samples were stored at $-80\text{ }^{\circ}\text{C}$ until analyzed.

2.4. Analysis of PFCs

The analyses of PFHxS, PFOS, PFOA, PFNA, PFDA, PFUnDA and perfluorododecanoic acid (PFDoDA) were performed by LC/MS/MS. Aliquots of 100 μ L serum were added with 10 μ L glucuronidase, 10 μ L ammonium acetate buffer, 10 μ L methylumbelliferyl- β -D-glucuronide and 25 μ L of a water:acetonitrile (50:50) solution containing ^{13}C - or ^{18}O -labeled internal standards for all evaluated compounds and digested at 37 $^{\circ}\text{C}$ for 90 min. The proteins were precipitated with 175 μ L acetonitrile and vigorously shaking for 30 min. The samples were thereafter centrifuged at 4200 g and 3 μ L of the supernatant was injected on a LC (UFLC^{XR}, SHIMADZU Corporation, Kyoto, Japan; LC/MS/MS) using hybrid triple quadrupole linear ion trap mass spectrometry equipped with a TurboIonSpray source (QTRAP 5500, Applied Biosystems). The column used was a C₈ column (4 μ m, 2.1 mm i.d. x 20 mm GENESIS; Grace Vydac, Hesperia, CA, USA). The mobile phase was A: 0.1% ammonia (NH₃) in water and B: 0.1% NH₃ in acetonitrile. The mobile phase was kept at 25% B for 1 min after injection. A gradient was then applied in 3 min to 95% B where it was kept for 1 min. The column was then conditioned at 25% B for 3 min. Air was used as nebulizer and auxiliary gas while pure nitrogen was used as curtain gas and collision gas. The temperature of the ion source was set at 500 $^{\circ}\text{C}$ and the declustering potential was -80 V. The MS analyses were carried out using selected reaction monitoring (SRM) in the negative ion mode. SRM transitions and collision energies (CE) used in the analysis are described in Table 2.

About 100 samples were analyzed in each batch. The results reported is the average of the two measurements from the same sample worked-up and analyzed on different days. These results were also used to calculate the reproducibility of the method (Table 2), determined as the coefficient of variation (CV) of the duplicate samples. The limits of

detection (LOD), determined as the concentrations corresponding to three times the standard deviation of the responses in chemical blanks, are also shown in Table 2. In all sample batches, the quality of the measurements was controlled by analyzing chemical blanks and in-house quality control samples, prepared from a large volume of serum spiked with small amounts of different PFCs. The analyses of PFOS and PFOA are part of the Round Robin inter-comparison program (Professor Dr. med. Hans Drexler, Institute and Out-Patient Clinic for Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg, Germany) with results within the tolerance limits, determined as three times the standard deviation of the results from special reference laboratories.

2.5. Statistics

For levels below the LOD the numbers obtained in the evaluation of the MS data were used assuming that these values also have some meaning. Mann-Whitney tests were used for pairwise comparisons of the PFC exposure concentrations between countries (Greenland vs Poland, Greenland vs Ukraine, and Poland vs Ukraine). Separate analyses for each population were performed regarding correlations between PFOS, PFOA and the other PFCs as well as evaluation of the impact of different determinants. The correlations between PFOS, PFOA and the other PFCs were evaluated by Spearman's correlation coefficients. The impact of potential determinants on inter-individual variations in PFOS and PFOA serum concentrations were assessed by linear regression models. As PFOS and PFOA were essentially normally distributed no transformation was performed. Model assumptions were checked by analysis of residuals. The determinants evaluated were age (continuous), BMI (continuous), smoking (categorical: never, ex-smoker and current smoker), seafood (days per week) and tea consumption (cups/day). In addition, the impact of area of residence was assessed for the

Greenlandic Inuits divided into three categories: (Mid: (Nuuk, Sisimiut, Maniitsoq and Paamiut), South/East: (Narsaq, Qaqortoq, Nanortalik, Tasiilaq, Kulusuk and Kuummiit) and North: (Kangaatsiaq, Aasiaat, Ilulissat, Qeqertarsuaq, Qasigiannuguit, Uummannaq, Qaanaaq, Illorsuit, Saattut and Ukkusissat).

The objective of the multivariate model building was to evaluate the impact of each of the determinants. In the first step we evaluated the associations for one determinant at a time with the PFOS and PFOA concentrations in serum, respectively. In the second step we included in the multivariate model all determinants with a p-value below 0.05 in the univariate analyses. However, if a determinant was statistically significant in one population but not in the others we present the univariate estimates also for the other countries. In the results we also give the explained variances (adjusted r^2 obtained from SPSSTM version 18 for the final models. To avoid ecological fallacies in these analyses, the three populations were analyzed separately.

3. Results

Concentrations of the analyzed PFCs are described in Table 3. With the exception of PFOA, the highest mean concentration for each PFC was found in the Greenlandic Inuit population, with the overall highest concentration displayed by PFOS (mean 52 ng mL⁻¹). The mean PFOS concentration in serum for the three regions in Greenland were: Mid: 44.7 ng mL⁻¹, South/East: 59.3 ng mL⁻¹, and North: 56.3 ng mL⁻¹. For PFOA, the Polish population had slightly higher concentrations than the Greenlandic Inuits. The dominating PFC in all three populations was PFOS with a fraction of 80%, 69% and 68%, of the total PFCs on weight basis, in Greenland, Poland and Ukraine, respectively. The second most dominating

PFC was PFOA with a fraction of 7%, 19% and 15%, respectively, for the three populations. Thus, PFOS and PFOA made up almost 90% of the PFCs in all three populations.

The numbers of samples below the LOD in the three populations are included in Table 3. For PFHxS, PFOS, PFOA and PFNA there were no or just a few samples below the LOD, for PFDA about half of the Ukraine samples were below the LOD, and for PFUnA and PFDoA the majority of the samples from Poland and Ukraine were below the LOD.

Correlations between PFOS and PFOA and the other PFCs in the three populations are included in Table 4. In the Greenlandic Inuit population there were high correlations between PFOS and most PFCs (r_s between 0.65 and 0.79) except for PFOA where the correlation was moderate ($r_s=0.42$). The correlations between PFOA and the other PFCs were lower ($r_s<0.30$). In the Ukrainian population there were moderate to high correlations ($r_s=0.39-0.72$) between PFCs, while the correlations between PFCs in the Polish population were low to moderate ($r_s=0.10-0.53$).

Among the Greenlandic Inuits, age, intake of tea and area of living were significantly associated with PFOS serum concentrations (Table 5). Together, they explained 19% of the variation. If we also included intake of seafood, the explained variance increased to 22%. Moreover, excluding one of the variables intake of seafood or area of living in the models did not change the estimate of the remaining variables, speaking in favor of these two variables as independent. In Poland, the only significant determinant was BMI and in Ukraine there was no statistically significant determinant. Regarding PFOA, the only significant association was observed for tea consumption among the Greenlandic Inuits. An increase of one cup per day corresponded to an increase in PFOA of 0.17 ng mL^{-1} (95% CI, 0.05, 0.29; $R^2=0.04$). Smoking was not associated with PFOS or PFOA.

4. Discussion

The present study provides data on levels of PFCs in populations for which such information is lacking or only scarce. The levels among Inuits in Greenland were among the highest described in the literature. Levels in Poland were similar to other industrialized populations while those in Ukraine were lower. Determinants found in most cases seemed to be similar to previous studies (Fromme et al. 2009, Haug et al., 2010a). However, the finding of different levels of PFOS in different areas of Greenland was novel. Also, the finding of tea consumption as a determinant for both PFOS and PFOA was not previously reported.

For the purpose of this study we developed a simple method for determination of several PFCs. The method uses only 0.1 mL serum and may therefore be suitable to apply on samples stored in serum banks. The coefficient of variation of duplicate samples worked-up and analyzed on different days was generally below 10% for duplicate analysis of the same sample, analyzed in different sample batches on different days. Moreover, the detection limits were sufficient for determination of levels in most samples. Furthermore, a high accuracy of the method, at least for PFOS and PFOA, was proven by participation in an inter-laboratory control program. However, it should be emphasized that a quantitative comparison of the presented data, especially with earlier published data, must be done with caution since there have been many challenges in the development of analytical methods for the PFCs over time (Martin et al., 2004).

The levels of PFOS in the Inuits on Greenland indicate that these are among the highest exposed populations in the world and was higher than those at 22 ng mL⁻¹ reported by Bonefeld-Jorgensen et al., (2011) for the controls in their study. This is in accordance with the high levels found in animals living in the Arctic area. Moreover, the results show that the Greenlandic Inuit population is highly exposed to several other, more recently industrially introduced PFCs, such as PFNA, PFDA, PFUnA and PFDoA. This indicates a fast

distribution of these compounds to the Arctic area. Interestingly, the levels of PFOA on Greenland were similar to the levels found in industrialized countries in Europe and the US.

Previous studies on Polish populations have found that people with a high consumption of fish from or residing by the Baltic Sea have considerably higher levels of PFCs than non-fish eating populations (Kannan et al., 2004; Falandysz et al., 2006). In the present study, the levels of PFCs in Poland were comparable to those found in Polish non-fish eating populations. This was to be expected, since the population was recruited from Warsaw, which is in the Polish inland, and did not have a high consumption of Baltic Sea fish. Some earlier pilot studies in Warsaw showed even somewhat lower levels of PFCs confirming lower exposure of inlanders (Struciński et al. 2006). The levels of PFCs in Poland were in the same range as for other industrialized countries (Fromme et al., 2009).

To the best of our knowledge, there are no previous reports of levels of PFCs in Ukraine. The levels found in this study indicate a rather low exposure compared to most industrialized countries. For PFOS the levels were similar to those at about 10 ng mL^{-1} found in Brazil and Colombia (Kannan et al., 2004).

Although PFOS correlated well with all other PFCs, except with PFOA, the correlations between PFOA and the other PFCs were low. One interpretation is that the exposure routes for PFOS differ from those for PFOA. E.g. difference in PFOS and PFOA fish concentrations has been observed that could indicate a lower potential of PFOA to bioaccumulate in fish than PFOS (Fromme et al. 2009). Thus, it is not surprising that we found different determinants for PFOA and PFOS.

We found significant determinants for PFOS only in the Greenlandic Inuit population. Possible explanations for this may include higher levels of PFOS among the Greenlandic Inuits than in Poland or Ukraine, but also a difference in exposure levels from the same exposure routes, e.g. that seafood consumed on Greenland carries a higher exposure than the

same amount consumed in Poland. Still, only 22% of the Greenlandic Inuit's PFOS levels were explained by the determinants investigated.

In the Greenlandic Inuit population, seafood was one of the determinants for PFOS. PFOS and – although to a lesser extent – PFOA have been found in both freshwater and marine fish species world wide (D'Hollander et al., 2010). Accordingly, studies relating fish and shellfish consumption to human levels of PFCs have generally found positive correlations (Falandysz et al., 2006; Rylander et al., 2009; Haug et al., 2010a), although not always for PFOA (Rylander et al., 2009). Thus, the results in the present study are in agreement with previous research.

Unfortunately we have no information regarding the Greenlandic Inuit's seafood consumption was related to consumption of fish or marine mammals. In some studies, consumption of marine mammals has been associated with high levels of PFCs in serum; Weihe et al. (2008) found a relationship between PFCs in serum of consumers of Faroese whale meat. In the present study, we found higher levels of PFOS but not PFOA in the remote areas of Greenland, where the diet tend to consist of more traditional Greenlandic Inuit food with consumption of fish and marine mammals, than in Nuuk, the capital of Greenland. Thus, the traditional Greenlandic Inuit food is most likely related to a higher exposure. In agreement with our study, Dallaire et al. (2009) did not find that the remote geographical location and traditional lifestyle protected the Canadian Nunavi Inuits from PFOS exposure.

Previous studies on a possible relationship between age and PFCs are inconclusive. Whereas some have found increasing levels of PFOS with increasing age (Olsen et al., 2005; Kärrman et al., 2006; Fromme et al., 2007; Rylander et al., 2009; Haug et al., 2010a), others have failed to show any age related changes for PFOS or PFOA (Harada et al., 2004, Kannan et al., 2004, Calafat et al., 2006, Jin et al., 2007, Olsen et al., 2008, Wilhelm et al., 2009). Similarly, in the present study, different results for age were found for the different PFCs and

the different populations. The influence of age on the levels of PFCs should be further investigated, especially considering that since environmental levels of PFCs have not been at a steady state during the past decades, age is not necessarily a proxy for exposure time.

In Poland there was an inverse relationship between PFOS and BMI. The effect estimate was similar in the Greenlandic population, although not statistically significant. A similar relationship has been found in the Danish general population (Eriksen et al., 2011) and a German population exposed to PFCs through contaminated drinking water (Holzer et al., 2008). However, other studies have not shown such an association (Halldorsson et al., 2008, Rylander et al., 2009). There was no expectation of finding an association with BMI since PFCs are mainly bound to proteins and not fat. We can therefore not rule out that in the Polish population, BMI is a proxy for an unmeasured determinant, such as diet.

It is interesting to note that tea seemed to be a determinant for PFOS and PFOA in the Greenlandic Inuit population. However, tea consumption was not a determinant of PFOS and PFOA level in Poland or Ukraine, with similar tea consumption as the Greenlandic Inuits. High levels of PFCs in tea could be a result of either high levels in the water with which the tea was brewed, from the tea leaves themselves or from the container (e.g. tea bag or tea infuser for home brewed tea or bottle for ready made tea, such as iced tea). Drinking water is generally not thought of as a major exposure source for PFCs. In most studies, its contribution to the daily intake of PFOS and PFOA has been found to be below 3% (Thompson et al., 2011). However, in some reports, it has been estimated to be as high as 55% (Noorlander et al., 2011; Thompson et al., 2011). We have found no reports on PFC levels in Greenlandic drinking water, and it is therefore difficult to draw any conclusions about the possibility that the water is the contributing factor the results found for tea consumption. In a study from Sri Lanka, workers from a rural conventional tea cultivation area had levels of PFOS and PFOA that were in the same range as people from the county's capital (Guruge et al., 2005). However,

workers involved in organic tea cultivation had considerably lower levels of both PFOS and PFOA. Thus, there is the possibility that something in the conventional tea cultivation might cause PFC contamination. Indeed, Haug et al. (2010) measured PFCs in a small sample of brewed tea, and found that the levels of PFOA but not PFOS were considerably higher in the prepared drink than in the water it was made from. Thus, it is possible that both water and tea leaves can contribute to the results found in this study.

5. Conclusion

The levels of PFCs in serum of Inuits on Greenland were among the highest described in a general population, whereas the levels in a population from Warsaw, Poland were similar to other industrialized countries. The levels in Ukraine were rather low. Determinants for PFOS on Greenland were seafood and tea intake, age and area of living. Tea was also a determinant of PFOA at Greenland. For the other populations no strong determinants were observed.

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Table 1. Background characteristics for 196 Inuit men (Greenland), 190 men from Warsaw (Poland), and 203 men from Kharkiv (Ukraine).

	Greenland	Poland	Ukraine
Age (yr)	30	30	25
Median (5 th , 95 th perc)	(20, 43)	(25, 37)	(19, 39)
BMI (kg m ⁻²)	25.5	25.4	24.0
Median (5 th , 95 th perc)	(20.4, 32.1)	(20.4, 31.8)	(19.6, 29.5)
Tea (cups/day)	2	2	2
Median (5 th , 95 th perc)	(0, 6)	(0, 5)	(1, 5)
Seafood (days/week)	2	1	4
Median (5 th , 95 th perc)	(0, 6)	(0, 3)	(2, 5)

Table 2.

Parameters for analysis, limit of detection levels and reproducibility^a for the analyzed compounds.

PFC	SRM transition	Collision energy (V)	Limit of detection (ng mL ⁻¹)	Reproducibility (%)	Concentration at reproducibility ^b (ng mL ⁻¹)
PFHxS	399/99	-80	0.06	8	1.5
PFOS	499/99	-85	0.2	5	26
PFOA	413/169	-25	0.6	6	3.9
PFNA	463/419	-15	0.2	9	1.6
PFDA	513/469	-16	0.2	9	0.6
PFUnA	563/519	-19	0.3	10	0.7
PFD _o A	613/569	-25	0.07	22	0.08
¹⁸ O ₂ -PFHxS	403/103	-80	-	-	-
¹³ C ₄ -PFOS	503/99	-110	-	-	-
¹³ C ₄ -PFOA	417/169	-30	-	-	-
¹³ C ₅ -PFNA	468/423	-15	-	-	-
¹³ C ₃ -PFDA	515/470	-16	-	-	-
¹³ C ₂ -PFUnA	565/520	-19	-	-	-
¹³ C ₂ -PFD _o A	615/570	-25	-	-	-

^a Determined as the coefficient of variation (CV) of duplicate samples worked-up and analyzed on different days.

^b The mean concentration for the samples from which the reproducibility was determined

Table 3: Concentrations (ng mL⁻¹) of the analyzed PFCs in Inuits from Greenland and inhabitants from Warsaw, Poland and Kharkiv, Ukraine and the number of samples below the limit of detection.

	Greenland	Poland	Ukraine
	n=196	n=190	n=203
PFHxS ^{a, b, c}			
Mean (SD)	2.88 (2.54)	1.22 (0.44)	0.40 (0.30)
Median (min, max)	2.18 (0.91, 20.5)	1.18 (0.43, 3.78)	0.34 (<LOD ^d , 3.42)
Samples below LOD	0	0	1
PFOS ^{a, b, c}			
Mean (SD)	51.9 (24.4)	18.6 (5.67)	8.08 (3.98)
Median (min, max)	44.7 (12.3, 161)	18.5 (8.20, 40.2)	7.60 (2.77, 29.9)
Samples below LOD	0	0	0
PFOA ^{b, c}			
Mean (SD)	4.83 (1.60)	5.25 (2.14)	1.79 (2.75)
Median (min, max)	4.54 (1.52, 13.7)	4.84 (1.48, 16.0)	1.29 (<LOD, 35.0)
Samples below LOD	0	0	16
PFNA ^{a, b, c}			
Mean (SD)	2.26 (1.74)	1.32 (0.69)	1.13 (0.54)
Median (min, max)	1.74 (0.53, 11.6)	1.19 (0.48, 6.11)	1.02 (0.25, 4.19)
Numbers below LOD	0	0	0
PFDA ^{a, b, c}			

Mean (SD)	1.08 (0.81)	0.41 (0.17)	0.23 (0.14)
Median (min, max)	0.87 (<LOD, 5.92)	0.38 (<LOD, 1.37)	0.21 (<LOD, 0.96)
Samples below LOD	2	11	99
PFUnDA ^{a, b}			
Mean (SD)	1.76 (1.74)		
Median (min, max)	1.28 (<LOD, 13.4)	<LOD (<LOD, 0.70)	<LOD (<LOD, 0.53)
Samples below LOD	11	168	178
PFD _o DA ^{a, b, c}			
Mean (SD)	0.19 (0.20)		
Median (min, max)	0.14 (<LOD, 1.68)	<LOD (<LOD, 0.23)	<LOD (<LOD, 0.10)
Samples below LOD	38	174	197

^a Significant difference ($p < 0.05$) between Greenland and Poland (Mann-Whitney test)

^b Significant difference ($p < 0.05$) between Greenland and Ukraine (Mann-Whitney test)

^c Significant difference ($p < 0.05$) between Poland and Ukraine (Mann-Whitney test)

^d Below the limit of detection

Table 4: Spearman's correlations coefficients^a (and p-values) between PFOS, PFOA and the other PFCs.

	Greenland		Warsaw (Poland)		Kharkiv (Ukraine)	
	n=196		n=190		n=203	
	PFOS	PFOA	PFOS	PFOA	PFOS	PFOA
PFHxS	0.65 (<0.001)	0.20 (0.01)	0.44 (<0.001)	0.23 (<0.001)	0.72 (<0.001)	0.49 (<0.001)
PFOA	0.42 (<0.001)		0.34 (<0.001)		0.56 (<0.001)	
PFNA	0.76 (<0.001)	0.18 (0.01)	0.43 (<0.001)	0.53 (<0.001)	0.57 (<0.001)	0.39 (<0.001)
PFDA	0.79 (<0.001)	0.16 (0.02)	0.37 (<0.001)	0.44 (<0.001)	-	-
PFUnDA	0.69 (<0.001)	0.05 (0.51)	-	-	-	-
PFDoDA	0.65 (<0.001)	0.04 (0.50)	-	-	-	-

^aCorrelation coefficients were only calculated when we had data above LOD for at least 60% of the participants.

Table 5. Linear regressions (univariate and multivariate models) for determinants for PFOS serum concentrations (ng/mL) among Inuit men (Greenland), Warsaw men (Poland), and Kharkiv men (Ukraine). Significant associations are marked with bold text. In addition, explained variances (R^2) are shown.

	Greenland			Poland			Ukraine	
	Univariate		Multivariate		Univariate		Univariate	
Determinants	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Age (yr)	0.87	(0.38, 1.4)	0.84	(0.36, 1.3)	0.062	(-0.14, 0.27)	-0.008	(-0.10, 0.087)
BMI (kg/m ²)	-0.37	(-1.2, 0.42)	-		-0.26	(-0.50, -0.014)	-0.003	(-0.18, 0.17)
Tea (cups/day)	2.6	(0.88, 4.2)	2.1	(0.52, 3.6)	0.38	(-0.21, 0.97)	-0.33	(-0.77, 0.10)
Seafood (days/week)	3.0	(1.1, 4.9)	2.1	(0.24, 3.9)	0.74	(-0.095, 1.6)	0.042	(-0.40, 0.48)
Area (North reference)								
South/East	3.0	(-6.0, 12)	0.67	(-8.0, 9.4)	-		-	
Mid	-12	(-20, -3.4)	-13	(-21, -5.8)	-		-	
Adjusted R ²			0.22		0.02 ^a		- ^b	

^a Including only BMI in the model

^b No significant associations