# Extractable organofluorine in human plasma

Authors: Welmoed Nauta[1], Ingela Helmfrid[2], Niclas Stensson[2], Stefan Ljunggren[2], Helen Karlsson[2] , Anna Kärrman[1]

[1] MTM Research Centre, School of Science and Technology, Örebro University
[2] Occupational and Environmental Medicine, Region Östergötland/Linköping University

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## Sammanfattning

Denna studie fokuserade på att mäta extraherbart organiskt fluor (EOF) i 24 blodprover från en kohort med hög- och lågfiskkonsumenter. Med hjälp av massbalansanalys jämfördes fluorkoncentrationen från den riktade PFAS analysen av 52 ämnen med EOF, vilket avslöjade en betydande mängd oidentifierad fluor i humanplasma.

Resultaten visade att EOF varierade från <10,1-21,9 till 1736 ng/mL F, med genomsnittlig och median koncentration i den höga fiskkonsumentgruppen på 214 respektive 25 ng/mL och i lågkonsumentgruppen 26 och 18 ng/ mL. Majoriteten av EOF kunde inte förklaras av identifierade PFAS i både hög- och lågfiskkonsumentgruppen, vilket tyder på närvaron av andra fluorföreningar. Variationer i EOF och fraktionen oidentifierat EOF observerades för både kön och fiskkonsumtionsvanor, även om ingen tydlig trend kunde identifieras.

## Summary

This study focused on measuring extractable organofluorine (EOF) in 24 blood samples from a cohort of high and low fish consumers. Using mass balance analysis, the fluorine concentration from the targeted PFAS (n=52) measured in the same plasma extract was calculated and compared with the EOF data, revealing a substantial amount of unidentified fluorine in human plasma.

Findings showed that EOF varied from <10.1-21.9 to 1736 ng/mL F, with average and median EOF concentration in the high fish consumer group of 214 and 25 ng/mL, respectively, and in the low consumer group 26 and 18 ng/mL, respectively. The majority of EOF could not be explained by identified PFAS in both high and low fish consumer groups, suggesting the presence of other organofluorine compounds. Variations in EOF levels and unidentified fraction were seen across gender and fish consumption habits, though no clear trend could be identified.

## Introduction

PFAS (per- and polyfluoroalkyl substances) are synthetic compounds used in a wide variety of consumer products for their non-stick, waterproof, greaseproof, stainproof, and low-friction properties due to their electronegative bonds (Buck et al., 2011). Products containing PFAS or PFAS coatings include carpets, glass, paper, clothing, other textiles, plastic articles, cookware, food packaging, electronics, and personal care products. Additionally, PFAS are used directly or as dispersants and emulsifiers in many industrial applications, including metal coatings, machinery lubricants, and firefighting foams.

The Organisation for Economic Co-operation and Development (OECD) revised their definition of PFAS in 2021, now including chemicals containing at least one saturated $-CF_2-$ or $-CF_3$ group (OECD 2021). This has resulted in growing numbers of PFAS in chemical inventory lists, reaching millions of different substances (Schymanski et al., 2023). Routine target analyses, however, typically include only the most used and identified compounds, mainly C4–C15 perfluorocarboxylic acids (PFCAs) and C4–C10 perfluorosulfonic acids (PFSAs) (Aro et al., 2022). The fluorine mass balance analysis has emerged as a promising technique for addressing the challenges of PFAS as a whole group by detection of fluorine, or extractable organofluorine (EOF), in combination with target PFAS analysis.

### *Aim*

The overall aim of the study was to estimate human exposure to PFAS through the consumption of fish caught in Swedish waters. To better understand the total amount of PFAS in human blood, analyses of extractable organofluorine (EOF) content were performed to serve as an additional metric alongside target PFAS analysis. The target PFAS results for the whole study are presented elsewhere (Helmfrid et al., 2024).

## Method

### *Sample information*

For this study, the population from the Glasbruket cohort (34,266 individuals) were selected. (Nyqvist et al., 2017) (Helmfrid et al., 2019). These individuals have lived at some point during their lifetime about 5 km from the glass industry. Approximately 800 individuals have provided both blood and urine samples and answered a questionnaire about housing, occupation, eating habits, illness and medication. Blood and urine samples have been collected between 2014 and 2018 and stored at minus 70 degrees in a biobank at Occupational and Environmental Medicine, Region Östergötland. High and low consumers of fish were selected from the cohort with 68 individuals from each group (matched age and gender). From these two groups a total of 24 samples were selected for EOF analysis, covering equal distribution between men, women, high- and low consumers of fish. The selection was further based on measured target PFAS concentrations and included individuals below the first quartile and above the third quartile (Helmfrid et al., 2024). An ethical permit for the project was granted by the ethical board (basic application Dnr 2009/138-31, amendment applications for extended studies of the environmental toxins POP, PAH, PFAS, Epigenetics and Proteomics in blood and urine Dnr: 2013/366-32, 2014/100-32, 2016/515-31, 2019/ 016-50 and Dnr 2020/03478).

### *Analysis of EOF*

For the EOF analysis, 3 mL of plasma was taken and extracted with 2 mL of 0.5 M tetrabutylammonium (TBA) solution in water and 5 mL of methyl tert-butyl ether (MTBE). (Aro et al., 2022). The mixture was shaken horizontally at 250 rpm for 15 minutes, centrifuged for 10 minutes at 8500 rpm (8000 g) and the supernatant was collected. The extraction was repeated twice with 3 mL MTBE. The collected extracts were combined and evaporated to 0.2 mL using nitrogen. Methanol was used to reconstitute the extract to 1 mL and it was evaporated again to a volume of 0.5 mL using nitrogen. The extract was quantitatively transferred to an LC vial using methanol to wash the PP tube and was then evaporated down to exactly 500 µL. For the CIC analysis, 150 µL was taken to determine the EOF content. Lastly, 100 µL was used for the target analysis for which the internal and recovery standards (10 µL of 0.2 ng mL−1 in methanol) were added to the extract, together with x 2 mM NH4Ac in water.

### *Mass balance analysis*

Target PFAS analysis (n=54, see Appendix A) was performed with an ultra-performance liquid chromatograph coupled to a tandem mass spectrometer (UPLC-MS/MS) system. The mass spectrometer used was a XEVO TQ-S triple quadrupole mass spectrometer (Waters Corporation, Milford, USA) with electrospray ionization (ESI) as ion source and all the samples were analysed in negative mode. The column was the Acquity UPLC BEH (Ethylene Bridged Hybrid) C18 column (1.7 µm particle size, 2.1 x 100 mm length). The separation of the targeted compounds was achieved by using mobile phase A) 2 mM ammonium acetate in MilliQ water and methanol (70/30 v/v) and mobile phase B) 2 mM ammonium acetate in methanol. For analysing PAPs, 5 mM of 1-methyl piperidine was added to the mobile phase.

To compare the data from the target analysis (ng/mL PFAS) with the EOF results (ng/mL F), the fluorine content of each target compound was calculated. This was done with Formula 1.

(1) $$C_F = n_F * \frac{MW\ F}{MW\ PFASi} * C\ PFASi$$

where CF is the concentration of fluoride (ng/mL F or ng/g F) of the analyte, nF is the number of fluorine atoms in the analyte molecule, MWF is the molecular weight of fluorine, MW PFASi is the molecular weight of the analyte, and C PFASi is the concentration of analyte (ng/mL PFAS or ng/g PFAS).

The fluorine mass balance can be calculated with Formula 2.

(2) $$C_{F\ unidentified} = C_{F\ OEF} - C_{F\ PFAS}$$

The total concentration of unidentified extractable organic fluorine (UOF) in ng/g F can be calculated by subtracting the concentration of fluorine from the target PFAS concentration from the EOF concentration.

## Results

### *EOF*

Of the 24 samples analysed for EOF, only 15 had an EOF level above LOQ, of which 53% were female and 60% belonged to the high fish consumer group (Figure 1). The LOQ ranged from 10.1 to 21.9 ng/mL in serum.

The EOF concentration ranged from <10.1-21.9 to 1736 ng/mL F, for details see Appendix B. The sample that gave the highest EOF concentration (male, high fish consumer) was diluted 20 times to be able to quantify with the external calibration curve (50 to 1000 ng/mL F). Average and median EOF concentrations in the high consumer group were 214 and 25 ng/mL, respectively, and in the low consumer group 26 and 18 ng/mL, respectively.

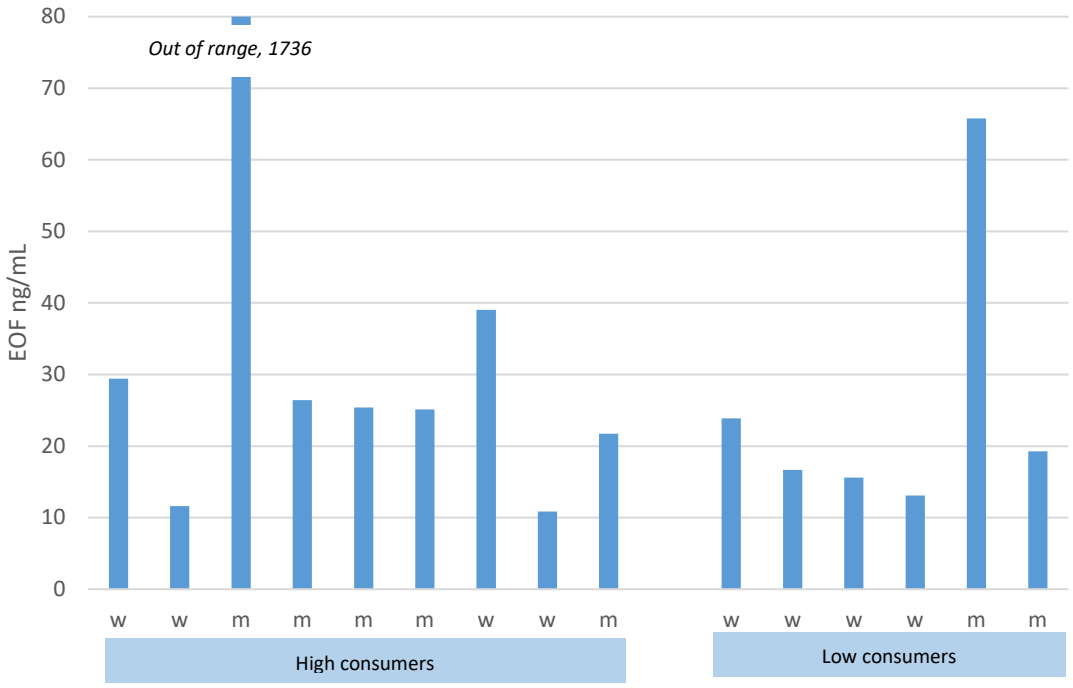


*Figure 1. Concentration of EOF (ng/mL) in plasma samples from women (w) and men (m) from high and low fish consumer groups*

### *Mass balance*

In Figure 2, the organofluorine mass balance is shown for the samples that were above LOQ. For the target PFAS analysis, the LOD ranged from 0.001 for PFNS to 0.05 ng/mL for PFOA. Target PFAS results were not recovery corrected and were converted to fluorine according to Formula 1. The unidentified organofluorine (UOF) was 0-99% (n=9) in the high fish consumer group and 56-94% (n=6) in the low consumer group. UOF was 68−94%) in female plasma and 0−99% in male plasma (Figure 2).

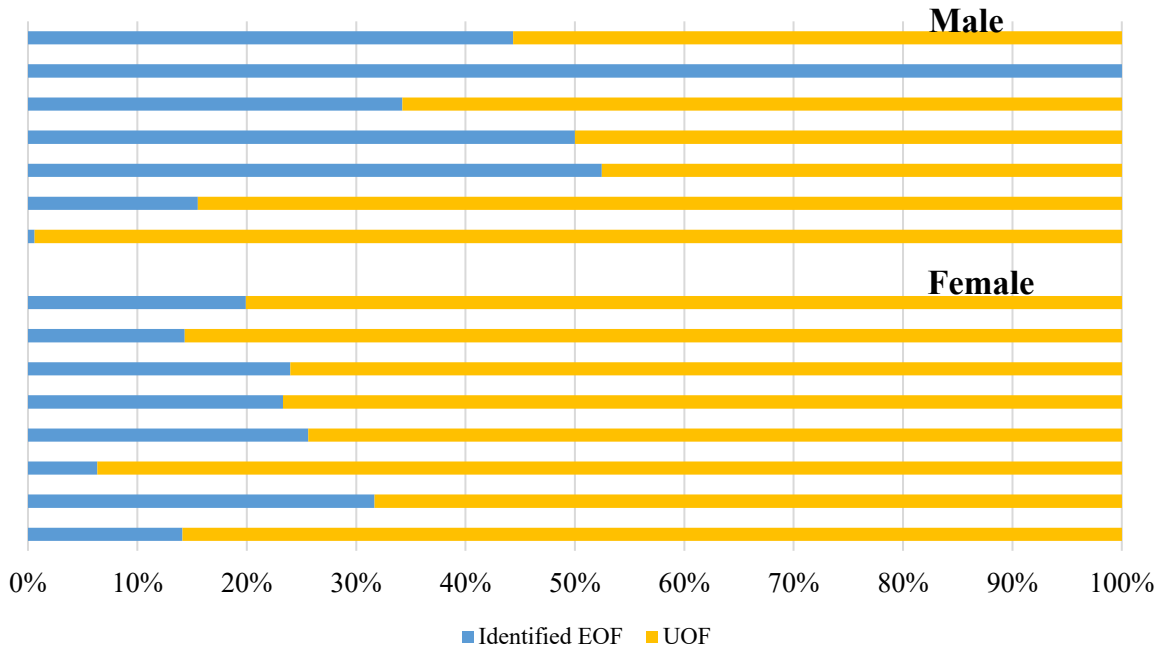


*Figure 2. Mass balance of concentration of EOF (ng/mL) and target PFAS (identified EOF) concentrations in plasma samples, revealing the fraction of unidentified organofluorine (UOF).*

## Discussion

The organofluorine mass balance analysis revealed that average 80.1% (range 68.3−93.7%) of the EOF in female plasma could not be explained by the 52 monitored PFAS. In males, 57.3% (0−99.4%) of the EOF was of unidentified origin. The two highest target compounds contributing to the identified EOF were PFOS and PFHxS. Previous study on EOF in Swedish whole blood samples collected from the general population in 2018-2019 showed an average concentration of 11 ng/ml for females and 6.4 ng/ml for males (Aro et al., 2021). The UOF in previous study was 60% and 41% for females and males, respectively. It should be noted that PFAS concentrations in whole blood has been shown to be lower compared to plasma or serum due to dilution of the plasma protein content (Poothong et al., 2017). The low detection frequency in this study (df 63%) could be increased if higher volume of plasma was extracted, or if lower blank contamination could be achieved.

A large part of the EOF content could not be identified with the targeted PFAS compounds included in the analysis in this study. The EOF method is non-specific and targets all fluorine and is therefore useful in screening for fluorinated compounds. Nowadays, a lot of drugs contain fluorine and there is an ongoing increase in the number of fluorinated pharmaceuticals on the market. The EOF analysis detects the extractable organofluorine and the presence of fluorinated pharmaceuticals in a sample may contribute to the EOF content. The information collected for the selected samples (Helmfrid et al., 2024) did not indicate that individuals used fluorinated pharmaceuticals, however there is an uncertainty if the survey questions included all fluorinated pharmaceuticals or if this information was filled in correctly. It should also be noted that ultrashort PFAS, like trifluoroacetic acid (TFA), were not included in the target analysis. These factors can explain the EOF levels that were measured and the low mass balance.

### *Conclusion*

No clear trend could be seen between males, females, high- or low consumer groups due to the large variation within the groups and the low number of samples with quantifiable EOF.

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## Appendix A

*List of compounds, including multiple reaction monitoring (MRM) transitions, cone voltage, collision energy and its corresponding internal standard used for quantification and qualification of PFAS for target analysis.*

| Compound | Precursor/ product ions quantification (m/z) | Cone (V) | Col (eV) | Precursor/ product ions qualification (m/z) | Cone (V) | Col (eV) | Internal Standard |
|---|---|---|---|---|---|---|---|
| **Precursors to perfluoroalkyl sulfonic acids** | | | | | | | |
| FOSA | 497.90/78.00 | 82 | 30 | 497.90/168.96 | 82 | 28 | $^{13}C_8$ FOSA |
| MeFOSA | 512/169 | 27 | 45 | - | - | - | $^{2}H_3$ MeFOSA |
| EtFOSA | 526/169 | 27 | 45 | - | - | - | $^{2}H_3$ MeFOSA |
| MeFOSE | 616/59 | 27 | 45 | 556.03/121.99 | 42 | 34 | $^{2}H_7$ MeFOSE |
| EtFOSE | 630/59 | 27 | 45 | 570.1/135.98 | 48 | 32 | $^{2}H_7$ MeFOSE |
| FOSAA | 555.84/482.76 | 60 | 26 | 555.84/418.85<br>555.84/218.90 | 60 | 24<br>30 | $^{2}H_5$ EtFOSAA |
| MeFOSAA | 569.78/418.87 | 16 | 18 | 569.78/482.76<br>569.78/511.92 | 16 | 14<br>22 | $^{2}H_5$ EtFOSAA |
| EtFOSAA | 583.84/418.84 | 18 | 20 | 583.84/482.80<br>583.84/525.88 | 18 | 16<br>20 | $^{2}H_5$ EtFOSAA |
| diSAmPAP | 1202.65/525.87 | 92 | 46 | 1202.65/168.90<br>1206.65/218.90 | 92 | 64<br>66 | $^{13}C_4$ 8:2 diPAP |
| **Perfluoroalkyl sulfonic acids (PFSAs)** | | | | | | | |
| PFBS | 298.90/98.90 | 20 | 26 | 298.90/79.96 | 20 | 26 | $^{13}C_3$ PFBS |
| PFPeS | 348.90/98.96 | 20 | 26 | 348.90/79.96 | 20 | 30 | $^{18}O_2$ PFHxS |
| PFHxS | 398.90/98.90 | 20 | 30 | 398.90/79.96 | 20 | 34 | $^{18}O_2$ PFHxS |
| PFHpS | 448.97/98.90 | 20 | 30 | 448.97/79.96 | 20 | 35 | $^{13}C_4$ PFOS |
| PFOS | 498.97/98.96 | 20 | 38 | 498.97/79.96<br>498.97/169.03 | 20 | 44<br>34 | $^{13}C_4$ PFOS |
| PFNS | 548.90/98.96 | 20 | 38 | 548.90.97/79.96 | 20 | 44 | $^{13}C_4$ PFOS |
| PFDS | 598.97/98.90 | 20 | 42 | 598.97/79.96 | 20 | 58 | $^{13}C_4$ PFOS |
| PFDoDS | 698.97/98.90 | 20 | 40 | 698.97/79.96 | 20 | 45 | $^{13}C_4$ PFOS |
| **Precursors of perfluoroalkyl carboxylic acids** | | | | | | | |
| 4:2 FTSA | 327.00/307.00 | 20 | 20 | 327.00/81.00 | 20 | 28 | $^{13}C_2$ 6:2 FTSA |
| 6:2 FTSA | 427.00/407.00 | 20 | 20 | 427.00/81.00 | 20 | 28 | $^{13}C_2$ 6:2 FTSA |
| 8:2 FTSA | 527.00/507.00 | 20 | 20 | 527.00/80.00 | 20 | 28 | $^{13}C_2$ 8:2 FTSA |
| 5:3 FTCA | 340.90/236.97 | 10 | 16 | 340.90/216.93 | 10 | 22 | $^{18}O_2$ PFHxS |
| 7:3 FTCA | 440.90/336.89 | 12 | 14 | 440.90/316.93 | 12 | 20 | $^{13}C_4$ PFOS |
| 6:2 monoPAP | 442.9/96.95 | 10 | 18 | 442.90/422.89 | 10 | 12 | $^{13}C_2$ 6:2monoPAP |
| 8:2 monoPAP | 542.9/97 | 22 | 14 | 542.90/522.90 | 22 | 14 | $^{13}C_2$ 8:2monoPAP |
| 10:2 monoPAP | 642.97/97.00 | 24 | 28 | 649.78/525.83 | 24 | 22 | $^{13}C_2$ 8:2monoPAP |
| 4:2 diPAP | 588.90/97.00 | 64 | 28 | 588.90/342.91 | 64 | 18 | $^{13}C_4$ 6:2 diPAP |
| 4:2/6:2 diPAPs | 688.90/97.00 | 64 | 28 | 688.90/342.91<br>688.90/442.91 | 64 | 18 | $^{13}C_4$ 6:2 diPAP |
| 2:2/8:2 diPAPs | 688.90/97.00 | 64 | 28 | 688.90/242.91<br>688.90/542.91 | 64 | 18 | $^{13}C_4$ 6:2 diPAP |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6:2 diPAP | 788.90/97.00 | 64 | 28 | 788.90/442.91 | 64 | 18 | $^{13}C_4$ 6:2 diPAP |
| 6:2/8:2 diPAP | 888.78/96.94 | 66 | 34 | 888.78/442.81<br>888.78/542.81 | 66 | 26 | $^{13}C_4$ 6:2 diPAP |
| **Perfluoroalkyl carboxylic acids (PFCAs)** | | | | | | | |
| PFBA | 212.97/169.00 | 20 | 11 | - | - | - | $^{13}C_4$ PFBA |
| PFPeA | 262.97/219.00 | 20 | 8 | - | - | - | $^{13}C_3$ PFPeA |
| PFHxA | 312.97/269.00 | 20 | 9 | 312.97/118.95 | 20 | 26 | $^{13}C_2$ PFHxA |
| PFHpA | 362.97/319.00 | 20 | 10 | 362.97/168.97 | 20 | 16 | $^{13}C_2$ PFHxA |
| PFOA | 412.97/369.00 | 20 | 10 | 412.97/168.97 | 20 | 18 | $^{13}C_4$ PFOA |
| PFNA | 462.99/419.00 | 20 | 12 | 462.99/219.00 | 20 | 18 | $^{13}C_5$ PFNA |
| PFDA | 512.97/469.00 | 20 | 11 | 512.97/219.00 | 20 | 18 | $^{13}C_2$ PFDA |
| PFUnDA | 562.97/519.00 | 20 | 12 | 562.97/268.99 | 20 | 18 | $^{13}C_2$ PFUnDA |
| PFDoDA | 612.97/569.00 | 34 | 14 | 612.97/168.96 | 40 | 22 | $^{13}C_2$ PFDoDA |
| PFTrDA | 662.90/619.00 | 20 | 14 | 662.90/168.96 | 20 | 26 | $^{13}C_2$ PFDoDA |
| PFTDA | 712.90/669.00 | 20 | 14 | 712.90/168.97 | 20 | 28 | $^{13}C_2$ PFTDA |
| PFHxDA | 812.90/769.00 | 30 | 15 | 812.90/168.96 | 42 | 32 | $^{13}C_2$ PFHxDA |
| PFOcDA | 912.90/869.00 | 36 | 15 | 912.90/168.96 | 36 | 36 | $^{13}C_2$ PFHxDA |
| **Perfluoroalkyl phosphinic acids (PFPiAs)** | | | | | | | |
| 6:6 PFPiA | 701.00/401.00 | 24 | 28 | - | - | - | $^{13}C_2$ PFDoDA |
| 6:8 PFPiA | 801.00/401.00 | 24 | 28 | 801.00/501.00 | 24 | 28 | $^{13}C_2$ PFTDA |
| 8:8 PFPiA | 901.00/501.00 | 24 | 28 | - | - | - | $^{13}C_2$ PFTDA |
| 6:10 PFPiA | 1001/401 | 24 | 28 | 1001/601 | 24 | 28 | $^{13}$C-PFDoDA |
| **Perfluoroethylcyclohexane sulfonic acid (PFECHS)** | | | | | | | |
| PFECHS | 460.84/381.00 | - | - | 460.84/98.88<br>460.84/180.96<br>460.84/168.94<br>460.84/118.96 | - | - | $^{13}C_4$ PFOA |
| **Perfluoropolyether carboxylic acids (PFECAs)** | | | | | | | |
| ADONA | 376.97/251.00 | - | - | - | - | - | $^{18}O_2$ PFHxS |
| HFPO-DA | 284.90/169.00 | - | - | - | - | - | $^{13}C_2$ PFHxA |
| **Polyfluorinated ether sulfonates (PFESAs)** | | | | | | | |
| 6:2 Cl-PFESA | 530.90/351.00 | - | - | 530.90/83.03<br>530.90/98.95 | - | - | $^{13}C_4$ PFOS |
| 8:2 Cl-PFESA | 630.90/451.00 | - | - | 630.90/98.95<br>630.90/83.03 | - | - | $^{13}C_4$ PFOS |

## Appendix B

*Concentrations of extractable organofluorine (EOF) amd target PFAS fluorine levels (ng F/mL) for plasma from women and men divided according to low and high fish consumption*

| Fish consumption | Gender group | EOF* (ng F/mL) | ∑Target PFAS (ng F/mL) | UOF (ng F/mL) | UOF (%) |
|---|---|---|---|---|---|
| high | women | 29,4 | 9,32 | 20,1 | 68% |
| high | women | 11,6 | 1,66 | 9,93 | 86% |
| high | men | 1735 | 10,5 | 1725 | 99% |
| high | men | 26,4 | 13,9 | 12,6 | 48% |
| high | men | 25,4 | 12,7 | 12,7 | 50% |
| high | men | 25,1 | 8,61 | 16,5 | 66% |
| high | women | 39,0 | 5,51 | 33,5 | 86% |
| high | women | 10,9 | 2,16 | 8,69 | 80% |
| high | men | 21,7 | 22,1 | -0,33 | -2% |
| high | women | <LOQ | 10,1 | - | - |
| high | women | <LOQ | 24,2 | - | - |
| high | women | <LOQ | 20,6 | - | - |
| | Average | 214 | 11,8 | 204 | 65% |
| | Median | 25,4 | 10,3 | 12,7 | 68% |
| low | women | 23,9 | 1,51 | 22,3 | 94% |
| low | women | 16,7 | 4,27 | 12,4 | 74% |
| low | women | 15,6 | 3,63 | 12,0 | 77% |
| low | women | 13,1 | 3,14 | 10,0 | 76% |
| low | men | 65,8 | 10,2 | 55,6 | 84% |
| low | men | 19,3 | 8,54 | 10,7 | 56% |
| low | men | <LOQ | 11,8 | - | - |
| low | women | <LOQ | 23,8 | - | - |
| low | men | <LOQ | 13,1 | - | - |
| low | women | <LOQ | 9,8 | - | - |
| low | men | <LOQ | 5,46 | - | - |
| low | men | <LOQ | 23,6 | - | - |
| | Average | 25,71 | 9,90 | 20,49 | 77% |
| | Median | 17,96 | 9,17 | 12,17 | 76% |

*The LOQ ranged from 10.1 to 21.9 ng/mL