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RESEARCH ARTICLE

Perfluoroalkane acids in human milk under the global monitoring plan of the Stockholm Convention on Persistent Organic Pollutants (2008–2019)

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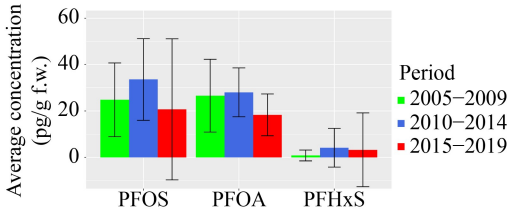
HIGHLIGHTS

- Perfluorooctanesulfonic acid and perfluorooctanoic acid highest in human milk.
- All other perfluoroalkane substances had median values of zero (101 samples).
- Branched PFOS recommended to be analyzed separately from linear isomer.
- PFOS and PFOA showed differentiated regional and income distribution.
- Human health risk assessment values not yet available at global level.

GRAPHIC ABSTRACT



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ABSTRACT

Within the global monitoring plan (GMP) established by article 16 of the Stockholm Convention on Persistent Organic Pollutants, perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS) are recommended for analysis in core matrices to assess occurrence and changes geographically and with time. In 101 samples consisting of 86 national pools and 15 pools from States in Brazil obtained between 2008 and 2019, PFHxS was detected in 17% of the national pools and none in Brazil. PFOA and PFOS had a detection frequency of 100% and 92%, respectively. Other perfluoroalkane substances (PFAS) had either low detection frequencies and median values of zero (carboxylic acids C_4–C_{11}; except PFOA) or could not be quantified in any sample (sulfonic acids, C_4–C_{10}, and long-chain carboxylic acids, C_{12}–C_{14}). Correlation between PFOA and PFOS was moderately (r = 0.58). Whereas median values were almost identical (18.9 pg/g f.w. for PFOS; 18.6 pg/g f.w. for PFOA), PFOS showed larger ranges (< 6.2 pg/g f.w.–212 pg/g f.w.) than PFOA (< 6.2 pg/g f.w.–63.4 pg/g f.w.). It was shown that wealthier countries had higher PFOA concentrations than poorer countries. No difference in concentrations was found for samples collected in countries having or not having ratified the Stockholm Convention amendments to list PFOS or PFOA. The goal to achieve 50% decrease in concentrations within ten years was met by Antigua and Barbuda, Kenya, and Nigeria for PFOS and by Antigua and Barbuda for PFOA. In a few cases, increases were observed; one country for PFOS, four countries for PFOA.

1 Introduction

Biomonitoring for polychlorinated dibenzodioxins and dibenzofurans (PCDD/PCDF) and polychlorinated biphenyls (PCB), to name two groups of the lipophilic organic pollutants has long traditions (WHO European Centre for Human Health, 1996; Yrjanheikki, 1989) and was continued with the global monitoring plan (GMP) under the Stockholm Convention on Persistent Organic

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Pollutants (UNEP, 2011; POPs, SC-5/18, Fifth Meeting of the Conference of the Parties). The aim of the GMP is to apply one framework for sampling and analysis of so-called core matrices to detect temporal and spatial changes of POP concentrations (UNEP, 2019c). Due to inherent persistence and bioaccumulation of chlorinated POPs, the biomonitoring samples should be collected from *primiparae*, *i.e.,* mothers having their first child, only. With this requirement, the influences of individual factors from the donor mother and the chemical, especially transformation but also detoxification through breast-feeding of a number of children, are reduced. Protocols to harmonize the identification, collection, and chemical analysis of the POPs in human milk had been developed and were updated periodically to incorporate newly listed POPs including the brominated flame retardants and perfluoroalkane substances (PFAS) (UNEP, 2017).

Perfluorooctane sulfonic acid (PFOS), its salts and perfluorooctane sulfonyl fluoride (PFOSF) was listed in 2009 (UNEP, 2009), amended in 2019 (UNEP, 2019a), perfluorooctanoic acid (PFOA), its salts and PFOA-related compounds was listed in 2019 (UNEP, 2019b). They have different physical and chemical properties than the initial chlorinated POPs and the later added polybrominated POPs (polybrominated diphenyl ether, hexabromocyclododecane, hexabromobiphenyl). They bind preferentially to proteins in the plasma (Han et al., 2003; Beesoon and Martin, 2015). Nevertheless, human milk remained the preferred matrix in the GMP and an aliquot from the national samples collected for the analysis of brominated/chlorinated POPs was recommended to be used for the analysis of the fluorinated POPs (UNEP, 2019c).

Perfluoroalkane substances (PFAS) are a group of persistent substances that is suspected to cause several negative health effects including reduced birth weight, late puberty and lowered semen quality (Fei et al., 2007; Joensen et al., 2009; Lopez-Espinosa et al., 2011; Rappazzo et al., 2017). In humans, often levels of perfluorocarboxylic acids (PFCA) and perfluorosulfonic acids (PFSA) but also fluorotelomer compounds or replacements such as ammonium 4,8-dioxa-3H-perfluorononanoate (CAS No: 958445-44-8, often referred to as ADONA), the ammonium salt of hexafluoropropylene oxide dimer acid (HFPO-DA) fluoride (CAS No: 958445-44-8, an emulgator in GenX) or 6:2 chlorinated polyfluorinated ether sulfonate (commercial name: F-53B) are monitored at global level. A recent study by Göckener et al. compared 2009–2019 human blood plasma samples from the German specimen bank with samples collected 1982–2010. It was found that PFOS and PFOA had not only a 100% detection frequency but also had the highest concentrations with 1.21 ng/mL–14.1 ng/mL for PFOS and 0.27 ng/mL–14.0 ng/mL for PFOA (Göckener et al., 2020) in these samples. Other PFAS, like perfluorohexanesulfonic acid (PFHxS) and perfluorononanoic acid (PFNA), had quite high detection frequencies but at lower concentrations (PFHxS: < LOQ–4.62 ng/mL; PFNA: < LOQ–3.66 ng/mL) than those of PFOS and PFOA.

Biomonitoring data using human milk are less than for blood, serum or plasma but have been reported from *primiparae* and *multiparae* (Fromme et al., 2010; Černá et al., 2020). Most human milk studies found concentrations in pg/g or pg/mL ranges for all PFAA analyzed, which showed much lower concentrations than those for human blood, which were in ng/mL range (Kärrman et al., 2006; Thompson et al., 2010). In all studies, PFOS and PFOA had the highest detection frequencies with some showing higher concentrations of PFOA than for PFOS (Jin et al., 2020); whereas other had PFOS dominating (Kärrman et al., 2010; Zheng et al., 2021). Two studies found the same levels for PFOS and PFOA (Liu et al., 2010; Sundström et al., 2011). Much higher concentrations at ng/g range were reported for PFOS in human milk samples from Italy (Guerranti et al., 2013). PFHxS was found at quite high concentrations in Swedish *primiparae* (Kärrman et al., 2007) and in mothers from Hangzhou, China (Jin et al., 2020).

Human biomonitoring measures chemicals, metabolites or other indicators as the absorbed dose in the human body. The human biomonitoring takes into account the chemical and physical properties of the substance, time of exposure as well as the individual factors such as uptake, metabolism, and excretion rates of the chemical. For a given compound, human biomonitoring can identify temporal or spatial trends but also lifestyle contributing factors and finally allow to identify populations at risk (WHO, 2015). The World Health Organization (WHO) report recommends analyzing existing human biomonitoring data for associations with country-level socioeconomic characteristics, such as gross domestic product (GDP) per capita.

This paper expands our previous publication containing the data for PFOS, PFOA, and PFHxS from 44 human milk samples (Fiedler and Sadia, 2021) to include other PFCA and PFSA, which are not included in the list of recommended POPs in the GMP guidance document (UNEP, 2019c). The results from historic stored samples (until collection year 2015 and including 18 local pool samples) from Brazil are also presented and discussed. In order to avoid bias due to different analytical methods employed, all samples were analyzed in spring 2020 using the laboratory's most sensitive PFAA analytical approach. The data reported here overwrite earlier values for the historic samples displayed in the graphic of the UNEP report (UNEP, 2013).

2 Materials and methods

2.1 Origin of samples and characterization

2.1.1 National and local pools

Sample collection, preparation of the pools and handling are described in the protocol developed by UNEP for the

human milk studies (UNEP, 2017) based on a WHO protocol (WHO, 2007), the GMP guidance document (UNEP, 2019c) and by Fiedler and Sadia (Fiedler and Sadia, 2021).

Also included is a subset of samples from Brazil, which were collected within a national project during 2011/2012. Sampling was performed according to the WHO guideline for developing a national protocol (WHO, 2007) and samples collected at human milk banks from the Brazilian National Network of Human Milk Banks. Sampling occurred in the year 2012 at 15 different state capitals of Brazil and ten individual samples were collected at each location. Three pooled samples according to "great regions" (GR1, GR2, and GR3) were prepared, each composed of 50 individual samples according to geographic locations. The characteristics of the individual pools as well as the three regional pools are included in Table S 9 in the supplementary information. For comparison between countries and across periods, the three samples from GR1, GR2, and GR3 are used.

Great Region 1 (GR1): Cuiabá/MT, Porto Velho/RO, Rio Branco/AC, Boa Vista/RR, Belém/PA;

Great Region 2 (GR2): São Luís/MA, João Pessoa/PB, Recife/PE, Maceió/AL, Salvador/BA;

Great Region 3 (GR3): Goiás/GO, Belo Horizonte/MG, Rio de Janeiro/RJ, São Paulo/SP, Florianópolis/SC.

2.1.2 Characterization of the samples

To account for transformation of the chemical molecule and limit lifestyle factors, the GMP limits the human milk matrix to *primiparae* collected between three and twelve weeks after delivery. In addition, mother and child should be healthy and only one baby fed (UNEP, 2017).

To assess spatial distribution, the countries were assigned to regions using the United Nations Regional Groups of Member States as African group (Africa), Asia-Pacific Group (Asia; with the Pacific Islands as a sub-group PAC), Central and Eastern Europe (CEE), Latin American and Caribbean Group (GRULAC) and Western European and Others Group (WEOG). The membership can be retrieved from the United Nations Website, Department for General Assembly and Conference Management (DGACM) (www.un.org/depts/DGACM/RegionalGroups.shtml). For convenience, the ISO-3 alpha codes are used in tables and figures instead of the full country name (ISO, No Year). For easier assessment of time trends, the sampling years were grouped into three 5-year periods (2005–2009, 2010–2014, 2015–2019). For lifestyle, global development indicators (World Bank, No Year-b) such as income (abbreviated as Word Bank classification, WBC) or population density (abbreviated as PD) were extracted from the World Bank Open Data Catalog (World Bank, No Year-a). The WBC or PD of the sampling year was assigned to each pool. The income classification is shown in Table S1 and expressed as gross national income (GNI) in current US dollar using the Atlas method. The population density is defined as population per square kilometer of land area (pop/km^2) and was grouped according to the latest definitions by the World Bank using the codes as shown in Table S2. As is common practice in the UN system, one parameter is assigned to the whole country (without local differentiation).

2.2 Chemical analysis

Ten mL of subsample from each national pool were received at random intervals at Örebro University and analyzed for PFOS, PFOA, and PFHxS as described in publications (Sadia et al., 2020; Fiedler and Sadia, 2021). In addition to the three Stockholm Convention PFAS, two perfluoroalkanesulfonic acids (PFSA), namely perfluorobutane sulfonic acid (PFBS) and perfluorodecanesulfonic acid (PFDS), and eight perfluorocarboxylic acids (PFCA), namely perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) were analyzed. Details on the composition of the mass-labelled extraction and injection standards are described in the publication by Sadia et al. (Table S2, (Sadia et al., 2020)). All standards were from Wellington Laboratories (Guelph, ON, Canada).

Aliquots of 2 g from the 10 mL subsamples were analyzed for PFAA by Örebro University, MTM Research Centre, Sweden. Prior to extraction, samples (2 g) did undergo alkaline digestion with sodium hydroxide, extraction was performed using acetonitrile and clean-up included weak-anion exchange solid-phase extraction and ENVI-Carb. Analysis was conducted with liquid chromatography coupled to mass spectrometry (LC-MS/MS). The detailed description of the analytical steps is provided in section "Chemical Analysis" of the Supplementary information and a graphical sketch shown in Fig. S1. Information on QA/QC samples and procedures are provided in the Supplementary information under "Chemical analysis" and have been described in two previous publications (Sadia et al., 2020; Fiedler and Sadia, 2021).

Average recoveries for mass-labelled standards in the samples, blanks and QC samples for other PFCA and PFSA was in the range 60%–106%. The MTM Laboratory had successfully participated in the 2nd, 3rd and 4th rounds of the UNEP-coordinated interlaboratory assessments for PFAS in the human milk test samples; e.g., z-score <|2| or within ±25% from assigned value for all PFAS compounds

that were assigned a *z*-score in the Round 4 of the 2018/2019 assessment (UNEP et al., 2017; Fiedler et al., 2020; UNEP et al., 2021; Fiedler et al., 2022).

2.3 Data handling and assessment

All data were maintained in Microsoft Office 365 Excel®; statistical evaluations and visualization were made using *R* packages (version 4.0.3) with R-Studio.

Non-parametric tests were undertaken since the data were not normal distributed. Spearman non-parametric correlation was applied to determine relationship between concentrations or percentage contribution of variables; the correlation coefficient r less than 0.05. The Kruskal-Wallis H test was used to determine if there are statistically significant differences between the independent variables and dependent variables. Post-hoc analysis was performed using the pairwise Wilcoxon test. Adjustment of the p-value was made using the Benjamini-Hochberg method. The significance values (p) for all tests were set to less than 0.05.

For all quantitative assessments, concentrations below the limit of quantification (LOQ) were set to zero; thus, lower-bound concentrations are given. All concentrations are reported in picogram per gram fresh weight (pg/g f.w.).

3 Results

3.1 General overview

The characteristics of all samples received according to country origin, sampling year, assignment to UN region, income, population density and sampling year are shown in Table S3. In total, 101 samples originating from 59 countries and collected between 2008 and 2019 have been analyzed for PFAA.

The number of samples (also as percentage of total) as provided from each of the UN regions, within each of the 5-year periods, income group, population density and ratification status are shown in Table S4. Among the 86 national pools, the regional distribution was not equal across all samples and had most of those originating from the African region (N = 27) followed by GRULAC (N = 21). Noteworthy is that 58% of the pools (N = 50) were collected in the most recent period (2015–2019). Further, the regional distribution within each of the three periods also varied largely; noteworthy, there was no sample from WEOG in the first period (2005–2009) and only one sample in the second period. Interestingly, the income groups (as WBC, as GNI per capita, in US dollar) were more balanced than the regional distribution; the two extremes, H and L, as high and low income, had the smallest shares whereas the upper-middle (UM) and lower-middle (LM) income groups were slightly more often represented. With respect to population density, almost half of the countries in GRULAC (48%) have less than 30.6 inhabitants/km^2 (A code) whereas in the other regions, the population density is more uniform.

With respect to governance, it can be seen that nine pools, corresponding to 10.5% of the results, were from countries that had not ratified the 2019 amendments to the Stockholm Convention Annexes to include PFOS and PFOA (UNEP, No year).

All measured PFAA values from the national pools are shown in Table S5 and Table S6 (these results are detailed in Section 3.6). PFOA was the only compound that was quantified in all samples (100% detection frequency). ΣPFOS was quantified with 92% (79 pools) whereby L-PFOS was quantified in 92% (LOQ = 6.2 pg/g f.w.) and br-PFOS in 84% of the samples (LOQ = 1.2 pg/g f.w.). The isomer-specific determination was made to account for potential sources of PFOS due to the widely applied production process by electrochemical fluorination (ECF). The candidate POP under consideration for listing, PFHxS, was quantified in only 17% of the samples (15 pools; LOQ = 5.5 pg/g f.w.). From the other PFAA, the highest detection frequency was found for PFBA with 48% (41 samples); however, it shall be noted that PFBA identification is based on retention with reference to authentic standard and a single MRM transition, whereas most of the PFAA, with the exception of PFPeA, have at least two MRM transitions for quantification. Detection frequencies for PFHxA and PFNA were 26% and 21%, respectively. For all these PFCA, the LOQ was 6.2 pg/g f.w. PFBS, PFDS, PFDoDA, PFTrDA, and PFTDA could not be quantified in any of the 86 samples at a LOQ of 6.2 pg/g f.w. These five PFAA are not considered further in the assessments.

The summary of descriptive statistics of the quantified PFAA for the 86 national pools is shown in Table 1.

Graphical sketches for the target PFAA are in Fig. 1. It shall be noted that although boxes can be seen for PFHxS, the median values in all regions are zero (see details in Table 1).

The maximum concentration for ΣPFOS, including the differentiation into L- and br-isomers and ΣPFOS, was found in the 2018 sample from Kiribati (KIR (2018)) in the most recent round of the survey, with 154 pg/g f.w, 57.8 pg/g f.w and 212 pg/g f.w. for L-PFOS, br-PFOS and ΣPFOS, respectively. The detection frequency for PFOS was 92% whereby all values < LOQ were encountered exclusively within the last round (2016–2019), the most recent samples. Figure 2 shows the concentrations of L-PFOS and br-PFOS in the UN regions (details in Table S5). In summary, the br-PFOS constitute up to 37% of the ΣPFOS with an average of 22% for individual pools; 24% when assessing the average values (5.77 pg/g f.w. *vs.* 24.4 pg/g f.w., Table 1). A total of 14 samples (16%) did not show quantifiable br-PFOS and seven (8% of total) of these did not have L-PFOS above LOQ.

For PFOA, the lowest value was found in the sample ETH (2019) with 6.20 pg/g f.w.; the maximum value of

Table 1 Descriptive statistics for all quantified PFAA in national pools according to compound and UN region (pg/g f.w.) ($N = 86$; SD = standard deviation; values at lower-bound)

PFAA	Africa ($N = 27$)	Asia ($N = 18$)	CEE ($N = 12$)	GRULAC ($N = 21$)	WEOG ($N = 8$)	Overall ($N = 86$)
ΣPFOS						
Mean (SD)	15.8 (10.7)	27.7 (46.7)	36.4 (22.1)	24.3 (18.3)	27.9 (13.5)	24.4 (26.0)
Median [Min, Max]	13.6 [0, 44.6]	16.2 [0, 212]	32.6 [12.2, 83.3]	18.4 [0, 65.3]	24.3 [13.5, 51.4]	18.9 [0, 212]
PFOA						
Mean (SD)	17.1 (10.4)	18.1 (7.17)	30.6 (9.16)	23.4 (12.6)	31.7 (13.4)	22.1 (11.7)
Median [Min, Max]	15.7 [6.20, 63.4]	17.4 [9.98, 35.0]	30.7 [12.6, 48.8]	19.7 [7.81, 61.5]	33.4 [17.7, 57.8]	18.6 [6.20, 63.4]
PFHxS						
Mean (SD)	0.489 (1.78)	6.90 (26.1)	2.37 (4.54)	2.61 (7.75)	4.28 (6.53)	2.96 (12.8)
Median [Min, Max]	0 [0, 7.56]	0 [0, 111]	0 [0, 12.9]	0 [0, 34.8]	0 [0, 17.4]	0 [0, 111]
L_PFOS						
Mean (SD)	12.4 (8.58)	21.9 (33.7)	28.4 (18.5)	17.4 (12.3)	20.4 (8.70)	18.6 (19.1)
Median [Min, Max]	11.5 [0, 37.5]	14.3 [0, 154]	24.0 [9.92, 70.5]	15.3 [0, 42.7]	18.1 [10.5, 36.3]	15.2 [0, 154]
br_PFOS						
Mean (SD)	3.43 (2.48)	5.72 (13.2)	7.97 (4.78)	6.88 (6.18)	7.56 (4.99)	5.77 (7.34)
Median [Min, Max]	3.16 [0, 8.06]	2.51 [0, 57.8]	6.39 [2.29, 18.3]	5.64 [0, 22.6]	5.46 [2.60, 15.1]	4.19 [0, 57.8]
PFBA						
Mean (SD)	54.7 (221)	60.6 (161)	32.3 (26.0)	22.6 (37.5)	4.23 (4.61)	40.3 (145)
Median [Min, Max]	0 [0, 1160]	7.78 [0, 688]	33.8 [0, 78.5]	0 [0, 113]	3.57 [0, 10.1]	0 [0, 1160]
PFPeA						
Mean (SD)	1.49 (3.70)		0.791 (2.74)	1.89 (8.67)		1.04 (4.84)
Median [Min, Max]	0 [0, 12.6]		0 [0, 9.49]	0 [0, 39.7]		0 [0, 39.7]
PFHxA						
Mean (SD)	6.76 (13.0)	3.98 (9.96)	8.07 (11.5)	11.5 (36.5)		6.89 (20.3)
Median [Min, Max]	0 [0, 45.8]	0 [0, 34.9]	2.64 [0, 31.7]	0 [0, 163]		0 [0, 163]
PFHpA						
Mean (SD)	1.06 (2.64)	1.08 (3.15)		1.04 (4.75)		0.811 (3.10)
Median [Min, Max]	0 [0, 9.24]	0 [0, 10.5]		0 [0, 21.8]		0 [0, 21.8]
PFNA						
Mean (SD)	0.654 (3.40)	2.52 (4.30)	5.57 (4.76)	1.26 (4.23)	3.18 (6.43)	2.11 (4.52)
Median [Min, Max]	0 [0, 17.7]	0 [0, 11.2]	6.42 [0, 14.8]	0 [0, 17.7]	0 [0, 17.5]	0 [0, 17.7]
PFDA						
Mean (SD)		0.930 (2.71)				0.195 (1.27)
Median [Min, Max]		0 [0, 8.68]				0 [0, 8.68]
PFUnDA						
Mean (SD)	0.243 (1.26)		0.599 (2.08)	0.340 (1.56)	0.775 (2.19)	0.315 (1.44)
Median [Min, Max]	0 [0, 6.57]		0 [0, 7.19]	0 [0, 7.13]	0 [0, 6.20]	0 [0, 7.19]

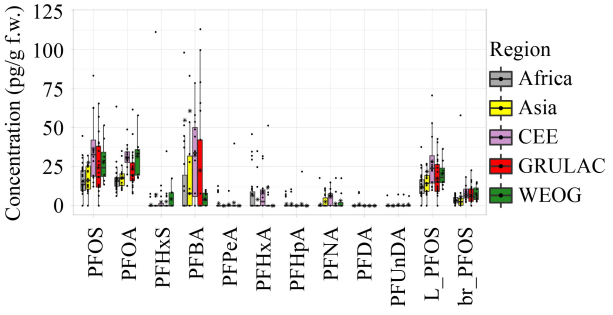

Fig. 1 Box plots for concentrations of all quantified PFAA according to the five regions (*y*-axis zoomed to 120 pg/g f.w); if not otherwise indicated 'PFOS' refers to the sum of L- and br-PFOS (N = 86).The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The asterisk represents the mean value. The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

63.4 pg/g f.w. was found in the national pool from Uganda, UGA (2009) followed by Chile (CHL (2008), 61.5 pg/g f.w.) and the Netherlands (NLD (2014), 57.8 pg/g f.w.). In contrast to the other two PFAA, PFOA in the Kiribati pool (KIR (2018)) was not among the ten highest (31.8 pg/g f.w.).

For PFHxS, the median value was zero (N = 86). KIR (2018) had also the highest concentration for PFHxS (112 pg/g f.w.), followed by Haiti (HTI (2011), 34.8 pg/g f.w.) and Sweden (SWE (2019), 17.4 pg/g f.w.).

The Kruskal Wallis test for the three Stockholm Convention PFAS revealed that there were significant differences between regions (p = 0.0042); the pairwise assessment shows that significant differences exist only when comparing Africa with CEE (p = 0.012) or WEOG (p = 0.019). All other pairwise tests have p-values between p = 0.080 (between Asia and CEE) and p = 0.92 (CEE with WEOG; which means that they are very similar).

Assessing PFOS (as ΣPFOS) and PFOA as separate variables, there were significant differences for both. Pairwise comparison for PFOS was detected only between Africa and CEE (p = 0.018) whereas for PFOA, there were significant differences for most combinations whereby the amounts found in WEOG were not significantly different from the values in CEE (p = 0.91) or GRULAC (p = 0.107). Largest differences were between Africa and CEE (p = 0.00038) or WEOG (p = 0.0017); also, Asian values were significantly different from CEE (p = 0.0067).

For all other quantified PFAA, the median values were zero. The highest mean value was for PFBA (40.3 pg/g f.w.); however, was accompanied by a large standard deviation (SD = 145 pg/g f.w.). The highest concentrations of PFBA with 1 160 ng/g f.w. and 688 ng/g f.w. were found in one African (UGA 2009) and one Asian pool (VNM 2019). The second highest mean value was for PFHxA (6.89 pg/g f.w., SD = 20.3 pg/g f.w.); the highest concentration was measured in the pool from CHL (2008), GRULAC region. Details are in Table S5. These compounds are not discussed further.

3.2 Time trends

Time trends on the concentrations of ΣPFOS, PFOA, and PFHxS according to the three 5-year periods are shown in Fig. 3(a); the highest mean and median values for all three compounds are in the second period (2010–2014). At Fig. 3(b), the concentrations of the three PFAA are grouped into the UN regions and the three 5-year periods. For the first period (2005–2009), no samples from WEOG were available and in the 2nd period, there was only one sample. In the African region, the mean and

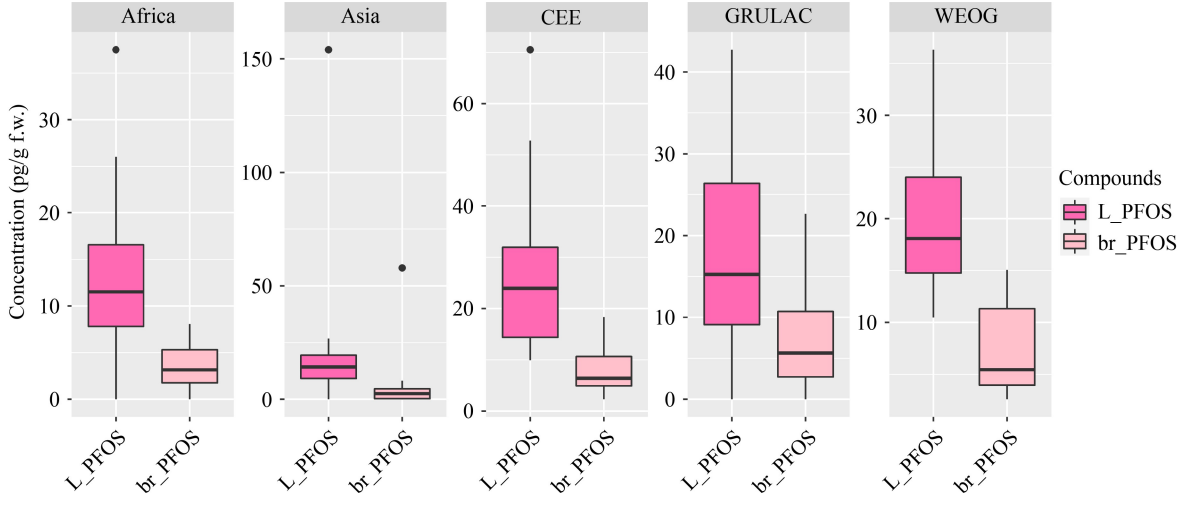

Fig. 2 Scaled box plots for concentrations of L-PFOS and br-PFOS according to regions (N = 86). Concentrations in pg/g f.w. The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

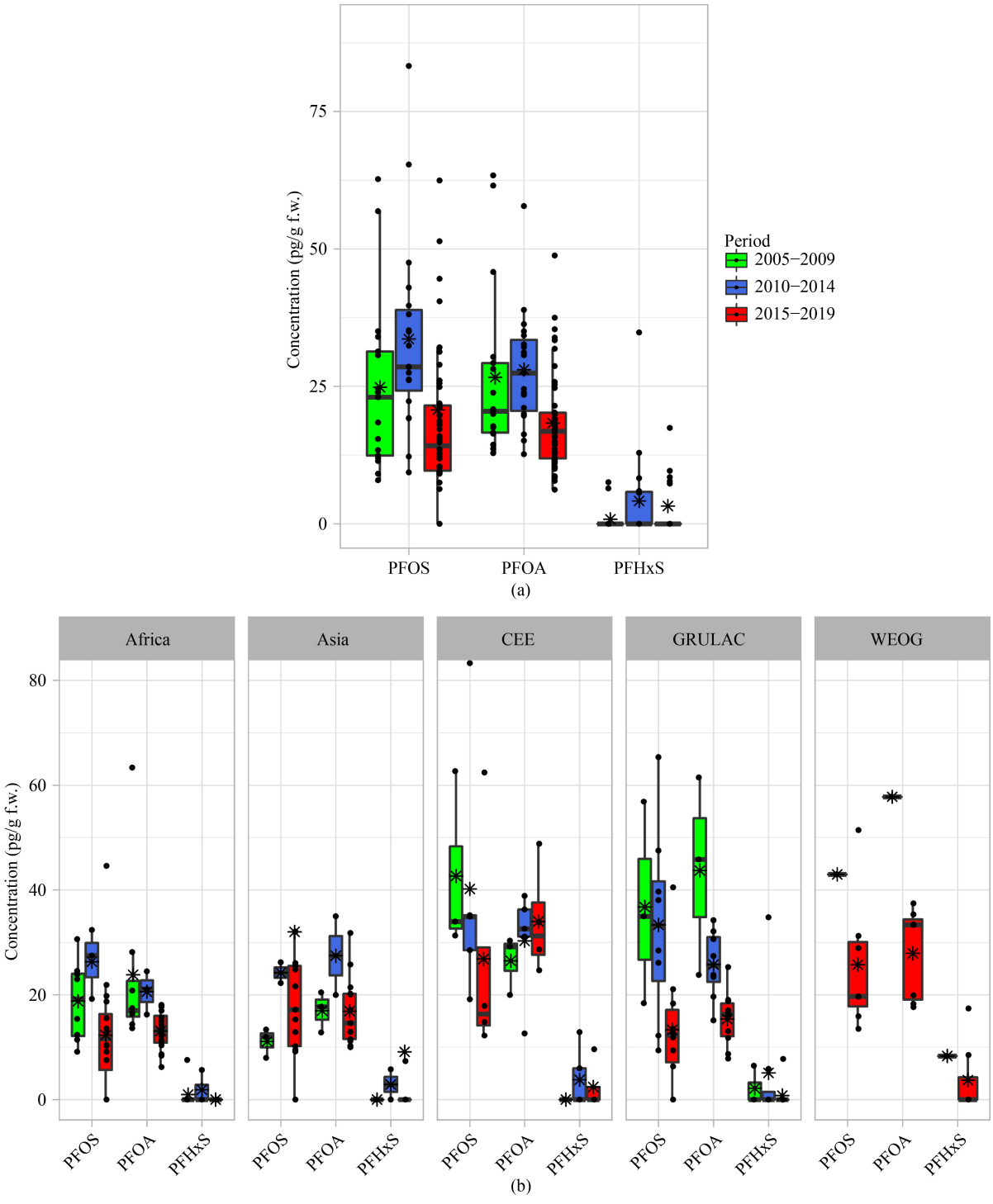

Fig. 3 Box plots for concentrations of three PFAA according to 5-year period (a); with differentiation into the UN regions (b) (N = 86); unscaled with y-axis zoomed to 80 pg/g f.w. The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The asterisk represents the mean value. The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

median values for ΣPFOS and PFOA were highest in the 2nd period (2010–2014); in GRULAC, only for ΣPFOS and for PFOA, the values were declining with time. Downward trends across the three periods can be seen for ΣPFOS in CEE and GRULAC and for PFOA in GRULAC. For details, see Table S7.

Assessing PFOS, PFOA, and PFHxS as variables together, statistically, there are significant differences with time (Kruskal-Wallis chi-squared = 13.973, p = 0.0009243) but only the 2nd period (2010–2014) was

significantly different from the third (2015–2019) with p = 0.00074. Assessing PFOS (as ΣPFOS) and PFOA as separate variables, it was concluded that for PFOA, the 1st period (2005–2009) was significantly different from the third (p = 0.029) and the second from the third (p = 0.00098) but there was no significant difference between 1st and 2nd periods (p = 0.228). For PFOS, only the amounts found in the 2nd period was significantly different from the values in the 3rd period (p = 0.00039).

3.3 Ratification

PFOS and PFOA are new POPs and parties must agree on amendments such as the listing of new POPs through official channels. The secretariat of the Basel, Rotterdam and Stockholm conventions maintains a website that mirrors the ratifications of amendments (UNEP, No year). With status of September 2021, 166 or 167 parties had ratified the 2019 amendments with respect to PFOS and PFOA. Among the countries that had submitted samples for human milk analysis, there were a total of six countries with nine samples that did not ratify these amendments: one party from Africa (Mauritius with two samples), two from Asia (India and Vanuatu with one sample, each), one from CEE (Moldova with two samples), and two from GRULAC (Argentina with one sample and Haiti, which is not a Party to the Stockholm Convention, with two samples). A comparison of the mean and median values with other statistical parameters is shown in Fig. 4 and values are provided in Table S8.

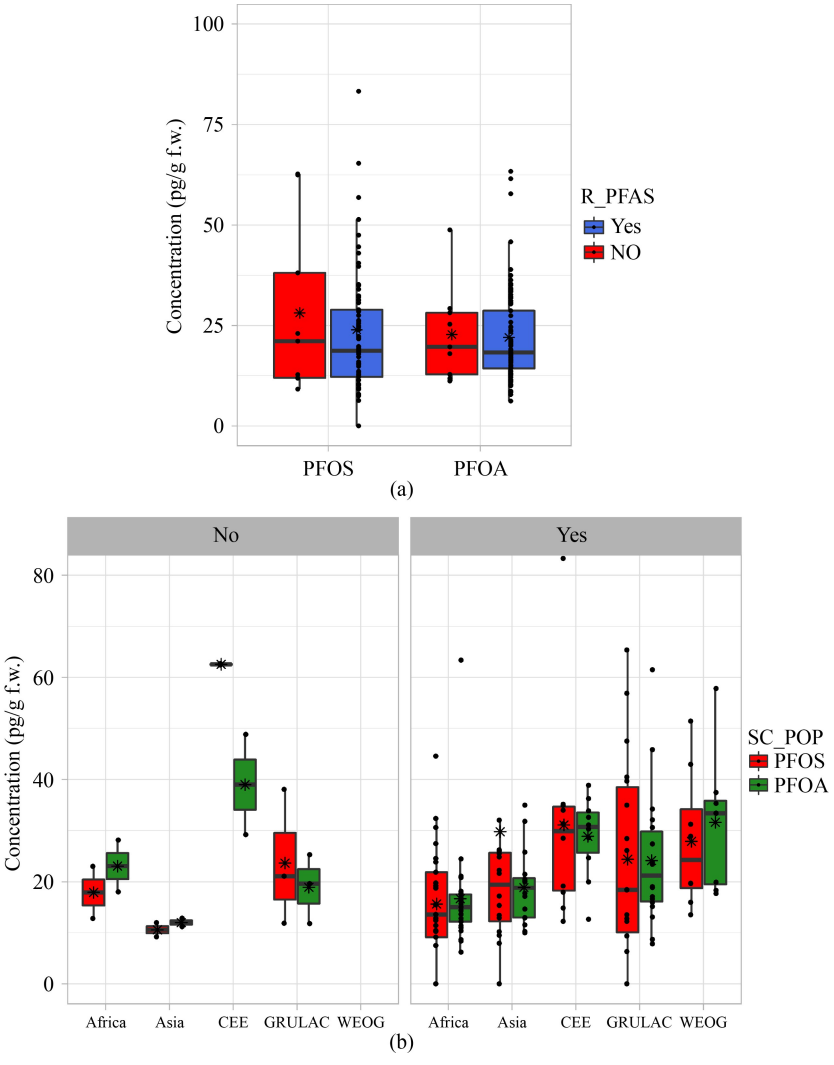

Fig. 4 Boxplots for ΣPFOS and PFOA concentrations in countries that ratified the PFOS and PFOA amendments to the Stockholm Convention ("Yes") and that did not ratify ("No") (unscaled with y-axis zoomed to 80 pg/g f.w., N = 86): (a) summary, (b) grouping according to UN regions. The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The asterisk represents the mean value. The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

With a *p*-value of 0.40, it cannot be concluded that a difference in human body burden is found between countries that ratified the legally binding agreement or not.

3.4 Income and population density

The assessment of POPs emissions in relation to GDP or GNI for socio-economic parameters in relation to the Stockholm Convention was presented earlier for PCDD/PCDF (Cao et al., 2013; Wang et al., 2016). It was found that higher PCDD/PCDF releases (as toxic equivalents) were associated with countries of large population. Nationwide low-income countries had higher emissions from open burning processes than higher income countries. No correlations were found between PCDD/PCDF emissions and land area.

The assessment for economic and lifestyle factors provides some further insight into our data. The assessment was done for the two legacy PFAA of high detection frequency in human milk, PFOS and PFOA.

For ΣPFOS and PFOA, the median values of the 86 pools are almost identical (18.9 pg/g f.w., 18.6 pg/g f.w.) whereas different mean values were observed with higher amounts for ΣPFOS (24.4 pg/g f.w., SD = 26.0 pg/g f.w.) than for PFOA (22.1 pg/g f.w., SD = 11.7 pg/g f.w.) (Table S11). For PFOA, the graphical sketches show that higher values correspond to higher incomes; for ΣPFOS,

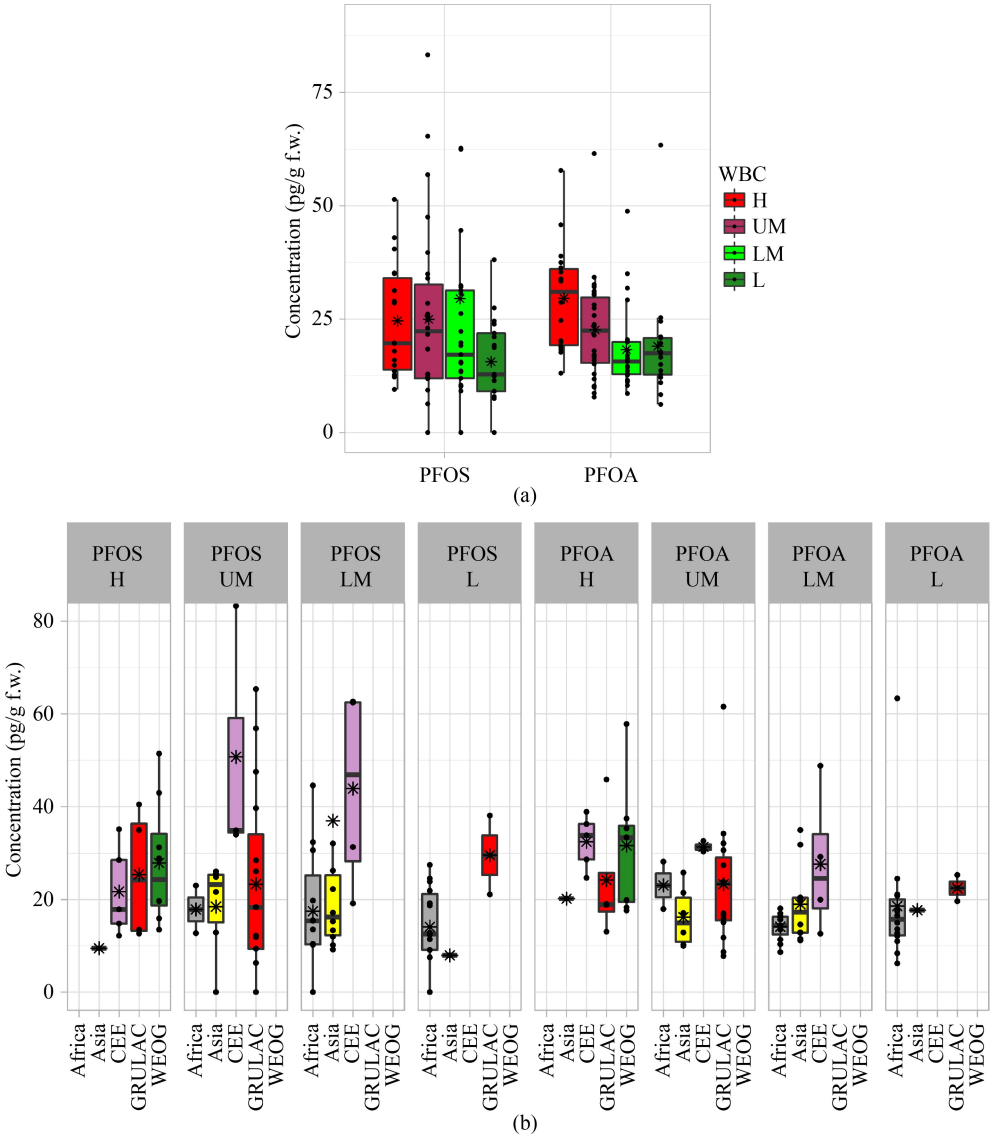

Fig. 5 Box plots for concentrations of ΣPFOS and PFOA (a) according to income (as WBC, unscaled with *y*-axis zoomed to 80 pg/g f.w) and (b) according to compound and WBC (unscaled boxplots) (*N* = 86). The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The asterisk represents the mean value. The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

no trend can be seen (Fig. 5). For population density, it cannot be concluded that densely populated countries have higher body burden of PFOS or PFOA (Fig. 6).

Spearman correlation between PFOS (as ΣPFOS) and PFOA was moderate (r = 0.58) when assessing these two variables together. Subsequently, both variables were evaluated separately for significant differences with respect to the UN regions, the three periods (2005–2009, 2010–2014, 2015–2019), income (as WBC) and population density (as PD_Code). With respect to population density, the Kruskal Wallis test did not find any significant differences between the groups for neither PFOS nor PFOA (p = 0.26 and p = 0.38, respectively).

For WBC, there was a statistically significant difference across all samples for PFOS and PFOA combined (p = 0.002872). When assessing PFOS and PFOA separately,

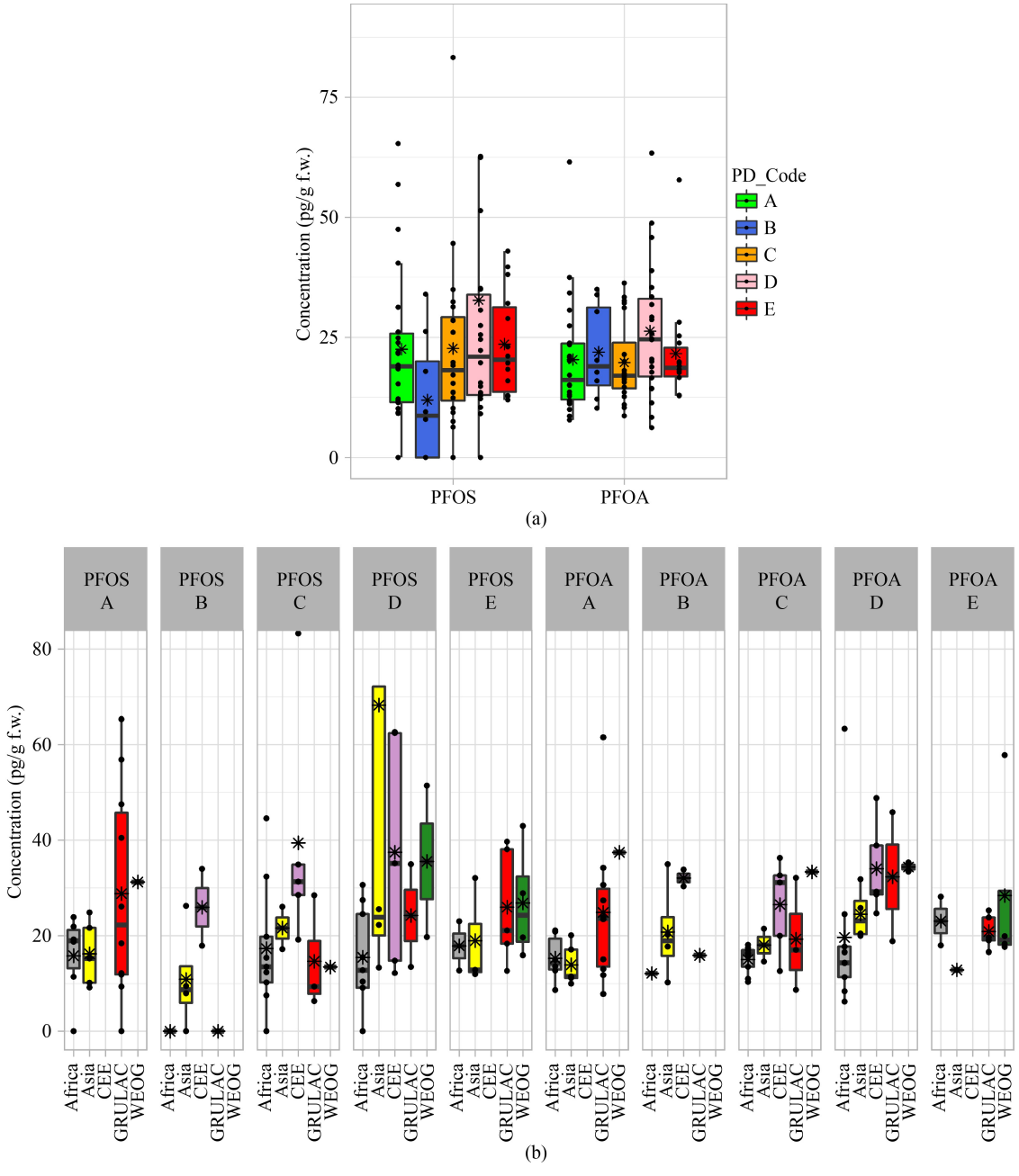

Fig. 6 Box plots for concentrations of ΣPFOS and PFOA (a) according to population density (as PD_Code, unscaled with y-axis zoomed to 80 pg/g f.w.) and (b) according to compound and PD_Code (unscaled boxplots) (N = 86). The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The asterisk represents the mean value. The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

the correlation for the WBC classification was not statistically significant for PFOS (p = 0.198) but highly significant for PFOA (p = 0.0013). The pairwise Wilcoxon test for PFOA stated that significant differences were for H with all other WBCs whereby the greatest difference was H *vs.* L (0.0068); the other combinations were smaller as countries became wealthier: H *vs.* LM (0.0027) and H *vs.* UM (0.0351).

3.5 GMP goal of 50% reduction in ten years

The GMP guidance stipulates the goal to achieve 50% reduction of POPs concentrations in the core matrices over a 10-year period (UNEP, 2019c). Among the 59 countries, there were 23 countries that participated in two different time periods. Barplots of the countries with two measured values are shown for ΣPFOS in Fig. S2 and for PFOA in Fig. S3 with the first measurement in the stronger colour (red for PFOS and forestgreen for PFOA) and for the second, more recent, measurement in the pale color (pink for ΣPFOS and green for PFOA).

From the 23 pairs, six had ten or more years between the samplings. To compare the temporal changes, concentrations at the first sampling were set zero and the change in concentration is calculated for a 10-year period. The results are shown in Fig. 7 ((a) for ΣPFOS; (b) for PFOA). The darker colors, red for PFOS and green for PFOA, indicate the six countries that had ⩾ 10 years between the samples (first six bars from Fig. 7(a)), the lighter color indicate shorter periods but normalized to 10-years whereby the six countries at Fig. 7(b) (lightest color; 18–23) had less than five years between the two samplings. The y-axis indicates decreases (negative values in percent) or increases (positive numbers in percent). It can be seen that more than 50% decrease of ΣPFOS concentrations was achieved in Kenya (KEN), Nigeria (NGA), and Antigua and Barbuda (ATG); for PFOA, only Antigua and Barbuda has achieved the 50% reduction goal. From the extrapolated results with present data available it would be implied that 12 more countries will achieve for ΣPFOS (UGA, COD, FJI, PER, JAM, TGO, LTU, MEX, CZE, GEO, HTI, and CHL) but only seven for PFOA (UGA, PER, MEX, CZE, GEO, NER, and CHL). More than 50% increase for ΣPFOS concentration would be found for Côte d'Ivoire (CIV) and no change for Moldova (MDA). For PFOA, strong increases would be found for Moldova (MDA) and Haiti (HTI), very small increases for Lithuania (LTU) and Côte d'Ivoire (CIV); Nigeria (NGA) seemed remaining unchanged.

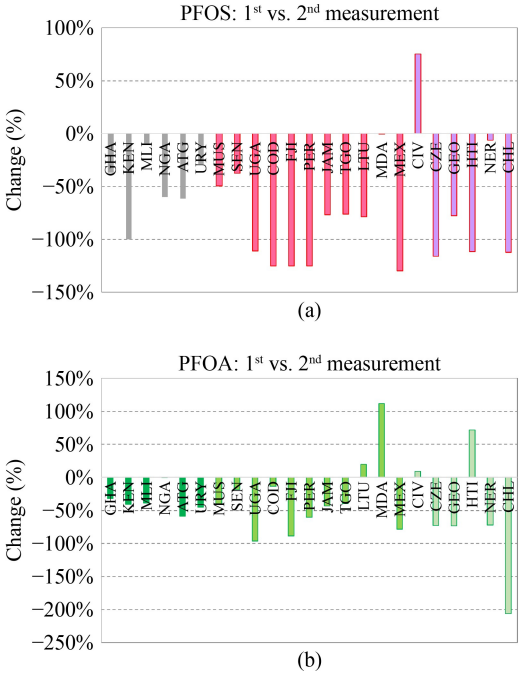

Fig. 7 Changes of concentrations in ΣPFOS (a) and PFOA (b) between samples; all percentages calculated to a period of 10 years (N = 23). In each figure, countries 1–6 refer to 10-year between samplings, countries 18–23 had ⩽ 5 years between samplings.

3.6 Brazil sub-samples

Brazil had implemented a more detailed sampling programme with subsamples from three Great regions (GR1, GR2, and GR3) as three pools and within each of them having five local pools. In total, 18 samples were analyzed and the individual results are included in Table S6. The graphical sketch of the four quantified PFAA, including L-PFOS and br-PFOS isomers, are shown in Fig. 8. Although there was a significant difference between GR1 and GR3 (p = 0.0003), there was no difference between GR pools (GR) and the pools therein (L) (p = 0.75). The Spearman correlation for ΣPFOS and PFOA gives R = 0.23 with p = 0.36; thus, no significant correlation for the variables.

Across all samples, PFHxS was not found at quantifiable amounts in any of the 18 samples (LOQ < 5.5 pg/g f.w.). Besides ΣPFOS and PFOA, PFHpA and PFNA were quantified twice at low concentrations (5.9 pg/g f.w. and 9.9 pg/g f.w. for PFHpA; 11.4 pg/g f.w. and 8.0 pg/g f.w. for PFNA).

The more detail study in Brazil allowed a closer look into possible bias within the samples. The descriptive statistics for the 18 Brazilian are displayed samples in Table S10 and the graphical sketch in Fig. S4. The concentrations of the Pools as GR1, GR2, and GR3 are better represented by the mean values of the respective local samples (L) than their median values.

4 Discussion

PFOS and PFOA were the first water-soluble POPs that were listed in the annexes of the Stockholm Convention on POPs. Although they do not follow the distribution pattern of the more lipophilic POPs such as the highly

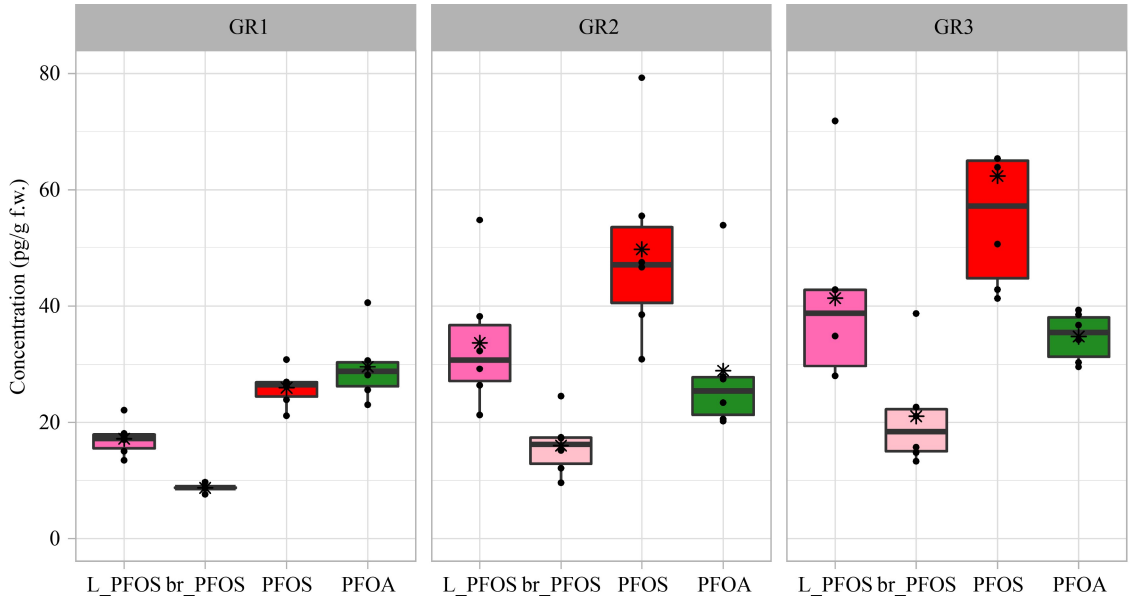

Fig. 8 Box plot for PFOS isomers, ΣPFOS, and PFOA according to great region (GR1, GR2, and GR3). Concentrations in pg/g f.w. The whiskers represent the minimum and maximum concentrations without the outliers. The lower border of the box represents the first quartile (25%), the line inside the box the median and the upper border is the third quartile (75%). The asterisk represents the mean value. The dots outside the whiskers are outliers, which were defined as all concentrations greater or smaller the interquartile range multiplied by 1.5.

brominated and chlorinated compounds and rather bind to proteins, the protocol for the human milk sampling and analysis as stipulated by the guidance for the global monitoring plan on persistent organic pollutants (GMP; UNEP, 2019c) was applied. As a consequence, and in contrast to the other POPs, concentrations of PFAA are reported on fresh weight basis (f.w.) and not on lipid basis. In total, 86 national pools from *primiparae* and an additional 15 sub-pools in Brazil were assessed on a regional and temporal basis as well as for lifestyle factors. Analysis and assessment included the two listed groups of PFAA, ΣPFOS and PFOA, PFHxS as a recommended compound, and other PFAA as a prognostic tool.

Multivariate analysis for the three Stockholm Convention compounds, shown as PCA plots in Fig. S5 in the Supplementary information, did not reveal information as to spatial (between regions) or temporal (between periods) trends. For all parameters, the ellipses did overlap largely. For the regional presentation, the Asia ellipse is driven by the outlier of the Kiribati sample. The spearman correlation plot showed that ΣPFOS and PFOA are not correlated and that there is no significance ($R = 0.23$, $p = 0.36$).

Analytically, the identification and quantification of the PFAA in human milk poses challenges but with an optimized method, it was possible to report PFOS and PFOA at a quantification limit of 6.2 pg/g f.w. and PFHxS at 5.5 pg/g f.w. These limits are comparable to those reported for Irish mothers analyzed with a time-of-flight mass spectrometer (Abdallah et al., 2020) or with a tandem mass spectrometer (like ours) (Jin et al., 2020) . PFOA was the most abundant compound and detected in all samples; PFOS had a detection frequency of 92% whereas PFHxS was quantified in only 17% of the samples; PFHxS was not found in any of the 18 samples from Brazil. The mean and median values for ΣPFOS and PFOA were comparable and no regional or time preference could be determined in this global survey. The pattern was clearly dominated by these two compounds. It was noted that the range of concentrations for ΣPFOS was much larger than for PFOA. Therefore, if decreases could be observed they were found preferentially for ΣPFOS and rarely for PFOA but only at country level.

The concentration for PFOA found in our sample from 2019, was 31.45 pg/g, which was much lower than those reported by Kärrman et al. who found 160 pg/mL in 1996 and 110 mg/mL in 2008 (31% reduction) (Kärrman et al., 2012) and the mean value of 74 pg/mL for 2008 (Sundström et al., 2011). The levels for PFOS, on the other hand, were comparable between the studies, for milk samples collected in 2011 an average content of 55 pg/mL was reported (range 28 pg/mL–132 pg/mL) and for samples in 2008 the mean value was 75 pg/mL. PFHxS was detected with a mean value of 14 pg/mL by Sundström et al. (2011), which corresponds to the reporting limit in this study. A declining trend in levels of both PFOA and PFOS has been reported in-breast milk. In a study from the Czech Republic, PFOA in breast milk was reported to decrease significantly from the median 75 pg/mL in 2006 to 23 pg/mL in 2017. PFOS also decreased from the median 45 pg/mL to 20 pg/mL (Černá et al., 2020). PFOA and PFOS showed statistically

significant decreasing values during 2001–2008 in human milk from Sweden (Sundström et al., 2011).

5 Conclusions

With this study, no spatial and temporal trends could be established mainly due to uneven representation of countries from the UN regions and relatively short time periods between the measurements. The Stockholm Convention goal of 50% reduction in ten years was achieved for PFOS by three countries (Kenya, Nigeria, and Antigua and Barbuda) and for PFOA by Antigua and Barbuda only. Extrapolation to ten years may imply that 12 more countries could achieve for PFOS but only seven countries for PFOA. Although some impact from geographic location (UN region) and lifestyle factors (income) were found, none of these seems to be a good indicator for PFOS and PFOA body burden.

Since there are no health-based values for PFOS and PFOA in human milk, present assessments remain limited to high quality analytical measurements and the interpretation of these results is limited to the assessment of geographic patterns. It is highly recommended to develop "safe" concentrations for PFOS and PFOA in human milk to support breastfeeding without risk as was done for PCDD/PCDF, PCB, and DDT (van den Berg et al., 2017).

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