Geographical differences in dietary exposure to perfluoroalkyl acids between manufacturing and application regions in China

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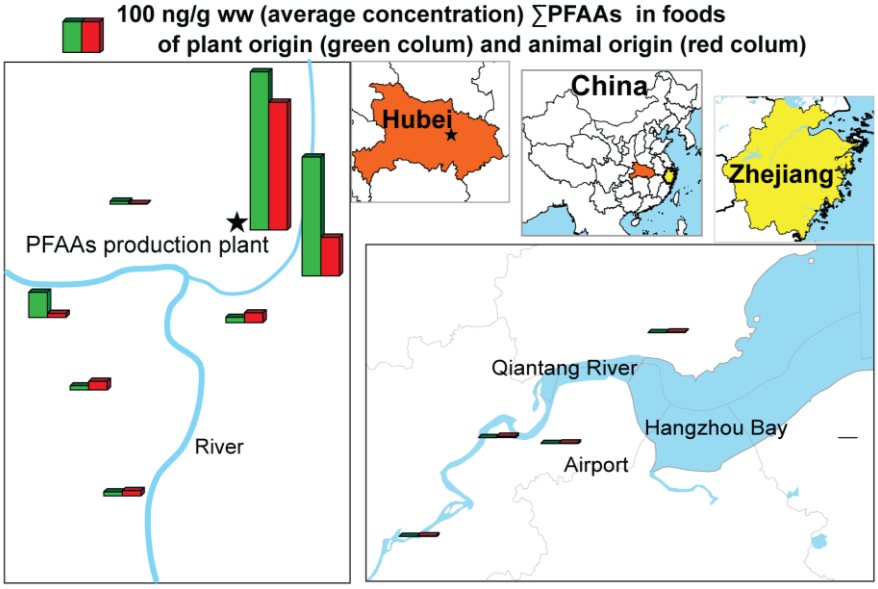
Abstract

Emissions of perfluoroalkyl acids (PFAAs) have increased in China over the past decade, but human exposure pathways are poorly understood. Here we analyzed 16 PFAAs in commonly consumed food items and calculated body weight normalized dietary intake rates (estimated dietary intake, EDIs) in an area with ongoing PFAA production (Hubei province; n=121) and an urbanized coastal area (Zhejiang province; n=106). Geographical differences in concentrations were primarily observed for perfluorooctane sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS) in animal food items and short-chain PFAAs in vegetable food items. The average EDI of ΣPFAAs for adults in Hubei (998 ng kg^{-1} day^{-1}) was more than two orders of magnitude higher than in Zhejiang (9.03 ng kg^{-1} day^{-1}). In Hubei province, the average EDI of PFOS for adults (87 ng kg^{-1} day^{-1}) was close to or exceeded advisory guidelines used in other countries indicating health risks for the population from long-term exposure. Yet, PFOS could only account for about 10% of the EDI of ΣPFAA in the Hubei province, which was dominated by short-chain PFAAs through consumption of vegetables. The large contribution of short-chain PFAAs to the total EDIs in manufacturing areas emphasize the need for improved exposure- and hazard assessment tools of these substances.

Graphical abstract



1. Introduction

Perfluoroalkyl acids (PFAAs) are a commercially important group of synthetic chemicals that contain a fully fluorinated carbon chain and an acid head group which is most commonly sulfonic acid (PFSA) or carboxylic acid (PFCA).[1] The combination of the perfluoroalkyl moiety and acidic functional group gives PFAAs unique surfactant properties and chemical stability which is useful in many industrial applications.[1] Although PFAAs have been produced in increasing quantities since the 1950s, it was only after the discoveries of perfluorooctane sulfonic acid (PFOS) in humans and wild-life that scientists and regulators started paying attention to their problematic environmental properties.[2] Long-chain PFSAs ($C_nF_{2n+1}SO_3H$, $n \geq 6$) and PFCAs ($C_nF_{2n+1}COOH$, $n \geq 7$) are of particular concern due to their environmental persistence, bioaccumulation potential and toxicity.[3]

Increased public awareness and stricter regulations in Europe and North America have led to a number of changes in PFAA production and use globally. In 2000-2002, the major global manufacturer of PFOS and related perfluorooctane sulfonyl fluoride (POSF) derivatives ceased production of these chemicals. More recently, a phase-out

strategy of perfluorooctanoic acid (PFOA) and related telomer-based derivatives was implemented by eight leading PFAA producing companies.[4] These phase-out actions have been partly accomplished by substituting long-chain PFAAs, such as PFOS and PFOA, with a variety of fluorinated alternatives which are typically shorter chain versions of their predecessors or per- or polyfluorether compounds.[5] The rationale for promoting the replacements is the lower bioaccumulation potential in aquatic organisms and more rapid elimination in mammalian species.[6-10] However, it remains widely debated whether or not these substances can be considered as safe alternatives.[11, 12] The little data which is available for per- and polyfluoroether acids suggest that they have a similar bioaccumulation as their corresponding PFAAs.[13, 14] Another important trend in the production and use of PFAAs is the continuous use of long-chain PFAAs in emerging economies such as China.[15, 16] An increasing number of studies have recently reported on the emissions of both legacy and replacement PFAAs from different parts of China,[17-19] but the impact of these emissions on human exposure remains poorly understood.

Exposure assessments from Europe and North America have identified dietary intake to be a major exposure pathway of PFOA and PFOS for the general population.[20, 21] However, the data sets on PFAAs in food items from China remain rather limited with most studies focusing on animal and dairy products.[22-27] In contrast to the typical western diet, the traditional Chinese diet is usually low in animal fat and high in dietary fiber with vegetables accounting for more than half of the dietary intake on a mass basis.[28, 29] Thus, consideration of dietary intake of PFAAs via vegetables may be particularly important in China compared to western countries. Considering the numerous ongoing point sources of PFAAs and varying dietary habits, there may also be large geographical differences in dietary exposure to PFAAs within China.

In this paper, we provide one of the most comprehensive dietary intake assessments of PFAAs from China to date. Specific emphasis was placed on elucidating geographical differences between PFAA manufacturing and application

areas and quantifying dietary exposure pathways for short-chain PFAAs. A large number of locally produced food items were collected from Hubei province (n = 121), and Zhejiang province (n = 106). The samples were analyzed for 15 perfluoroalkyl acids as well as perfluorooctane sulfonamide (PFOSA), and combined with regional food consumption statistics to estimate the total dietary intake.

2. Experimental Section

2.1. Sample collection

Hubei and Zhejiang province in China were selected for this sampling campaign due to their difference in production and use patterns (Figure 1). Hubei is the major province for production of PFOS and related chemicals in China.[15] The sampling area from Hubei included one of the largest facilities of PFOS and PFOS-derivatives in China. In contrast, Zhejiang province has little documented production of PFASs. As a densely populated and highly industrialized coastal province there are, however, multiple potential applications of PFAAs in textile and leather treatment, metal plating, fluoropolymer manufacture and fire-fighting foams at airports (e.g. Xiaoshan Airport which is marked in Figure 1.[15, 30] Emission inventories of PFOA and PFOS further suggest that diffuse emissions are relatively more important in Zhejiang compared to Hubei province.[15, 31]

A total of 227 samples of commonly consumed food items were collected in the two provinces during the period of September to November 2012. More than 20 different food types of plant origin were included and grouped into 4 different food categories; cereals (n = 9), tubers (n = 8), legumes (n = 13) and other leafy vegetables (n = 100). Food items of animal origin included livestock meat (n = 6), poultry meat (n = 30), offal (edible livers of pork, duck and chicken, n = 22), eggs (n = 14), fish (n =18) and fish liver (not commonly consumed in China, n = 7) (for further details, see Table S1 in the Supporting Information). Most of the food samples were directly collected from the households and farms of local residents. Crops were washed with tap-water to remove dust or soil from the surface. Free range chicken and ducks were

purchased from the local residents and sacrificed on place. Their meat and liver was removed and wrapped in aluminum foil. Livestock meat (pork and beef) and pork liver were purchased from local markets in the villages. Fish samples were captured from rivers near the villages or purchased from the local market. All the samples were wrapped in aluminum foil, placed into different plastic bags, and then transported to the laboratory. Only edible parts of all samples (after peeling off or cutting the roots) were homogenized using a kitchen blender and thereafter freeze-dried, then stored in a fridge at -20 °C until sample pretreatment and analysis.

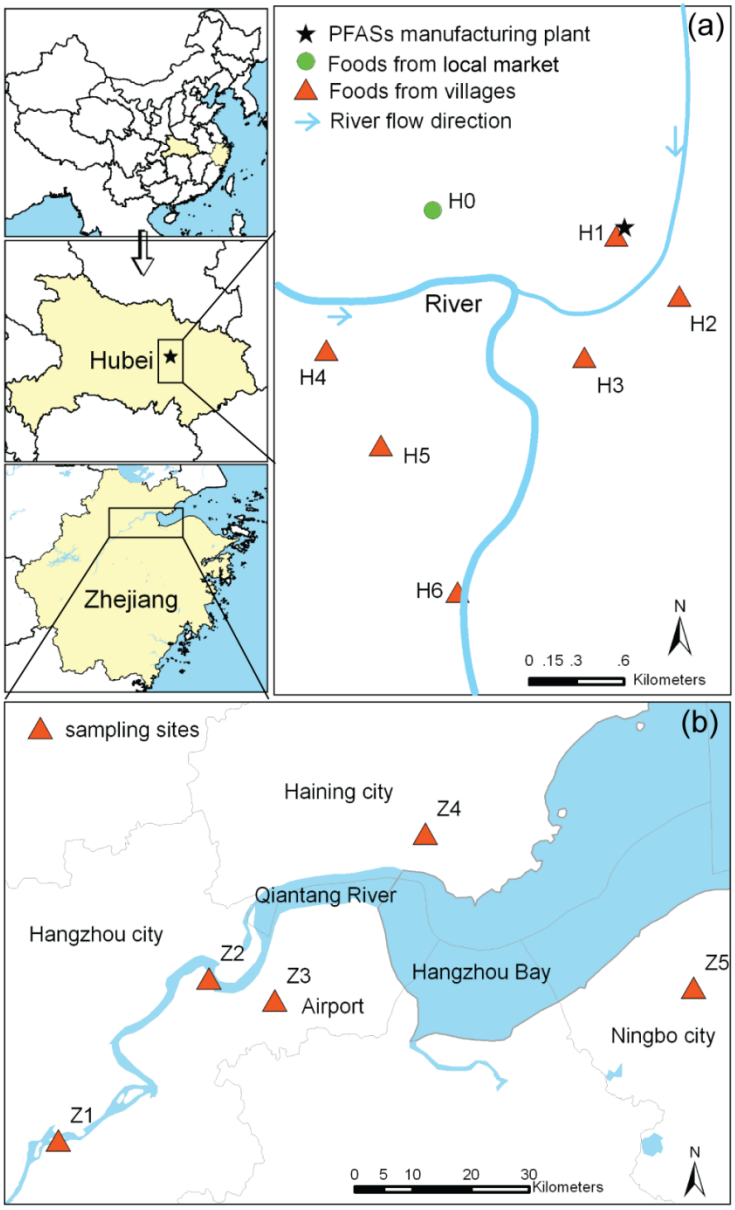


Figure 1. Sampling sites in (a) Hubei and (b) Zhejiang provinces

2.2. Chemicals and materials

All standards were purchased from Wellington Laboratories (Guelph, ON, Canada). The 16 analytes included 4 PFSAs (PFBS, PFHxS, branched and linear PFOS (brPFOS, linPFOS), perfluorodecane sulfonic acid (PFDcS)), 11 PFCAs (perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDcA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorotetradecanoic acid (PFTeDA)), and perfluorooctane sulfonamide (PFOSA). Isotope labeled internal standards (IS) included [$^{13}C_4$]-PFBA, [$^{13}C_2$]-PFHxA, [$^{13}C_4$]-PFOA, [$^{13}C_5$]-PFNA, [$^{13}C_2$]-PFDcA, [$^{13}C_2$]-PFUnDA, [$^{13}C_2$]-PFDoDA, [^{18}O]-PFHxS, [$^{13}C_4$]-PFOS, and [$^{13}C_8$]-PFOSA were applied as mass-labelled internal standards (IS) (Table S2), all donated by Wellington Laboratories (Guelph, Canada), and branched perfluorodecanoic acid (brPFDcA) was used an injection standard.

All solvents and reagents were of HPLC grade (Merck-Schuchardt, Hohenbrunn, Germany). A Milli-Q system (Millipore, Billerica, MA) was used and the generated water was further passed through a mixed mode C8 plus quaternary amine (CUQAX) SPE cartridge. Florisil sorbent (60/100 mesh) and graphitized carbon (Supelclean ENVI-Carb, 120/400 mesh) were purchased from Supelco (Bellefonte, PA). Florisil sorbent was dried at 450 °C overnight and deactivated with HPLC water at 0.5% (w/w) before usage.

2.3. Extraction and clean up

The freeze-dried samples and field blank samples were transported to Norwegian Institute for Air Research (NILU) in Norway for subsequent pretreatment and analysis. The extraction and clean-up protocol was based on the method described by Vestergren et al.[32] with some minor modification. In short, approximately 1 g dry weight of food sample was weighted into a 50 mL polypropylene (PP) tube. Isotope

labeled internal standards (2.5 ng) and 6 mL of 400 mM NaOH was added and the sample was allowed to equilibrate at 4 °C overnight. Thereafter, 4 mL tetrabutyl ammonium hydrogen sulfate (TBA) solution, 8 mL 250 mM Na_2CO_3/$NaHCO_3$ buffer, and 10 mL methyl tertbutyl ether (MTBE) were added and the mixture was vortexed for 30 s. The samples were extracted in an ultrasonic bath at room temperature for 10 min and phase separation was carried out by centrifugation at 3500 rpm (4110 G) for 10 min. The organic phase was then transferred to a 15 mL PP tube. The extraction was repeated twice with 5 mL MTBE for each extraction. The extracts were combined and concentrated to a final volume of approximately 1 mL using a Rapidvap nitrogen evaporation system (Labconco). A 5 mL disposable glass pipette with a glass wool plug was used for clean-up, and was filled with 1.5 g of Florisil mixed with 25 mg of ENVI-carb at the bottom and 1 g of anhydrous granular Na_2SO_4 at the top. The column was rinsed with 5 mL of methanol (MeOH) and then conditioned with 5 mL of MTBE. Thereafter, the sample extract was loaded and the column was washed with 10 mL of MTBE. Subsequently, the target analytes were eluted with 10 mL of a 30/70 MeOH/MTBE mixture (v/v). The eluate was evaporated to ~500 µL using Rapidvap after which 2 ng brPFDcA standard was added. The final solution was stored in a refrigerator until analysis.

2.4. Instrumental methods

100 µL of the final solution was mixed with 100 µL of 2 mM NH_4OAc for instrumental analysis. The instrumental analysis method for PFAAs was performed by an ultrahigh pressure liquid chromatograph coupled with a triple–quadrupole mass-spectrometer (UHPLC-MS/MS) according to Hanssen et al.[33] Analysis was performed on a Thermo Scientific Vantage MS/MS (Vantage TSQ) (Thermo Fisher Scientific Inc., Waltham, MA, USA); using a Waters Acquity UPLC HSS 3 T column (2.1× 100 mm, 1,8 µm) (Waters Corporation, Milford, MA, USA) equipped with a Waters Van guard HSS T3 guard column (2.1× 5 mm, 1.8 µm) (Waters Corporation, Milford, MA, USA). Separation was achieved using 2 mM NH_4OAc in 90:10

187 water/MeOH (A) and 2 mM NH_4OAc in MeOH (B) as the mobile phases. A Waters
188 XBridge C18 column (2.1× 50 mm, 5 μm) (Waters Corporation, Milford, MA, USA)
189 was installed after the pump and before the injector. The analytical conditions, parent
190 ions, monitored transitions, collision energies and S-lens are shown in Table S3.
191 Quantification was conducted using the LCQuan software from Thermo Scientific
192 (Version 2.6) (Thermo Fisher Scientific Inc., Waltham, MA, USA).

193 **2.5. QA/QC**

194 An internal standard method using isotopic dilution was emplyed to ensure
195 accurate identification and quantification of the analytes. Isotope labeled PFAAs were
196 used for all analytes except PFPA, PFHpA, PFTrDA, PFTeDA and PFBS. For these
197 analytes the closest isotope labelled PFCAs or PFSAs based on retention time
198 standard was used for quantification. Peaks with a signal-to-noise ratio (S/N) > 3 were
199 identified based on the retention time compared with the corresponding standards.
200 Field blanks were deployed at each region by opening a clean polypropylene
201 container filled with anhydrous sodium sulfate at the sampling site for about 2 hours.
202 Freeze drying blanks (anhydrous sodium sulfate added to freeze frying batches) and
203 extraction procedural blanks were used to assess potential field and laboratory
204 contamination. Limit of quantitation (LOQ) was defined as values of the lowest
205 detectable calibration standard corresponding to the peak with S/N ≥ 10. For PFAAs
206 with no detectable blank contamination, LOQ was used to calculate the method limit
207 of detection (MDL). For PFAAs with detectable concentrations in procedural or field
208 blanks; these were used to define the MDL as the arithmetic mean plus three times the
209 standard deviation of blank values. MDLs were in the range 0.01−0.07 ng/g for most
210 PFAAs and PFOSA, except for brPFOS and PFDcS which had MDLs ranged from
211 0.14 to 0.33 ng/g. Trace amounts of PFBS and PFBA were found in the field and
212 freeze drying blanks for Hubei samples, and the MDLs for these two analytes were
213 calculated to 0.23 and 0.17 ng/g respectively. More details of LOQ and MDL are
214 shown in Table S4. The recoveries for surrogate standard of [^{13}C]-PFAAs ranged

from 54% ± 29% to 96% ± 25% (Table S5). All the results reported in this study were reported on a wet weight basis and were not blank corrected. Accuracy and precision was evaluated by the authors by analysing a reference material consisting of pig liver, fish muscle and pea homogenate supplied by the KBBE EU project PERFOOD, compliancy of the currently used methods were reported by the authors to and published by Weiss et al..[34] The analytical method utilized by us achieved Z-scores between 0.06 and 1.4 for 12 target PFAAs.[35] A subset of samples (n = 9) with high concentrations of PFBA and PFPA were selected for re-analysis using UPLC-qTOF MS at Stockholm University according to the method established by Ullah et al.[36] to confirm the identification of these analytes by accurate mass since they do not have a qualifier ion in MS/MS. All results confirmed the positive detection and quantification of these PFAA.

2.6. Dietary intake calculations

For calculation of total dietary intake the individual food items were grouped into different food categories (as described above). The body weight normalized estimated daily intake of PFAAs (*EDI*; ng kg^{-1} day^{-1}) was subsequently calculated by the following equation

$$EDI = \frac{\sum_{i=1}^{n} C_{food,i} \times q_{food,i}}{B_w}$$

Where $C_{food,i}$ is the average concentration of the respective PFAAs in each food category (ng g^{-1} wet weight), $q_{food,i}$ the estimated quantity of food consumed per day of that a specific food category (g day^{-1}) and B_w is the body weight (kg). The average daily intake of each food category for male adults in the two investigated regions and adults at different ages [29] are shown in Table S6 and Table S7, respectively. For censored concentration data, we applied a lower bound (LB) and upper bound (UB) approach where non-detects were assigned as zero or half the MDL respectively.

2.7. Statistical analysis

Statistical analysis was performed using PASW V18.0 (SPSS Inc) and Excel (Microsoft Inc). Differences in concentrations of PFAAs in the food categories from the different regions were evaluated using non-parametric Mann-Whitney test. Correlation analysis was performed with Spearman's rank correlation coefficient (ρ). Tests showing significance levels < 0.05 were considered as statistically significant.

3. Results and discussion

3.1. Concentrations in food items

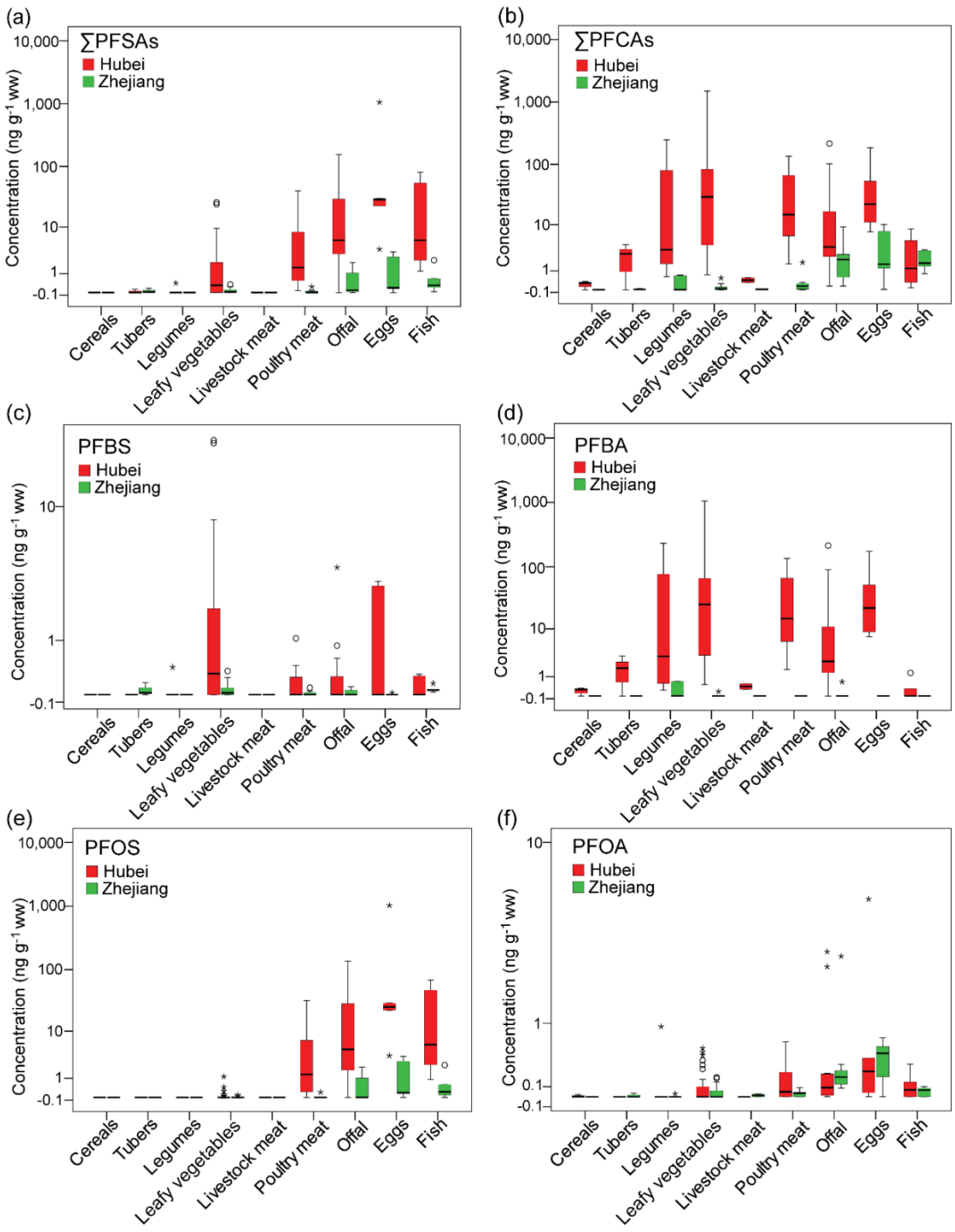
Detection frequencies (DFs) of PFAAs varied greatly among the different food categories and sampling locations (see Table S8). Overall, long-chain PFCAs including PFOA, PFNA, PFUnDA, PFDoDA and PFTrDA were detected in eggs, fish, fish liver and other offals at comparable frequencies between the two provinces (DF ≥50%) whereas short-chain PFCAs and PFBS were primarily detected in leafy vegetables, legumes and tubers from Hubei province (DF >67%). PFOS displayed a high detection frequency (DF ≥78%) in eggs, fish and fish liver from both sampling locations while PFHxS was most frequently detected in animal food samples from Hubei province. PFDcS and PFOSA were below detection limits in the majority of samples (DF <3%) and thus were not included in the following discussion.

Total concentrations of ∑PFAAs from both sampling locations displayed large variability, but were considerably higher in all food categories from Hubei (range, average, median: <MDL−1523, 97.3, 12.8 ng g^{-1} ww), compared to Zhejiang (<MDL−14.3, 1.71, 0.17 ng g^{-1} ww) (Figure 2 and Figure S1). Concentrations of ∑PFSAs were generally higher in foods of animal origin while the highest concentrations of ∑PFCAs were detected in foods of plant origin (Figure 2). The findings of PFOS and long-chain PFCAs as the predominant compounds in fish samples are well in line with the positive relationship between perfluoroalkyl chain-length and bioaccumulation potential in the aquatic environment.[6, 37] A similar PFAA profile in other animal food products including eggs, offal and poultry provide

support to recent studies showing that PFOS and some long-chain PFCAs also bioaccumulate in terrestrial agricultural food chains.[38-40] The higher levels in eggs and offal food compared to meat are further consistent with preferential distribution to the liver and eggs compared to muscle tissue.[41, 42] The distinct PFAA profile in leafy vegetables (PFBA>PFPA>PFBS>PFHxA>PFHpA>>long-chain PFAAs) compared to animal food items indicate that other mechanisms are responsible for the accumulation of PFAAs in edible parts of plants leading to subsequent human exposure. In contrast to food items from animal products, where increasing hydrophobicity and proteinophilicity leads to slow elimination,[6, 43] the high water solubility of short-chain homologues facilitates efficient uptake from pore water and translocation within the plant.[44-48] As the water evaporates, the anionic and non-volatile PFAAs will subsequently be enriched in the plant material.[44-48] Interestingly, the levels of PFAAs in leafy vegetables (Chinese cabbage, leek, spinach, greens, Chinese kale) were higher than those in tubers (white radish, carrot, sweet potato) and fruit vegetables (tomato, pumpkin, hot pepper) with exception of hyacinth bean. Thus, the measured concentrations of short-chain PFAAs are generally consistent with controlled uptake experiments showing that the evapotranspiration at the leaves lead to the highest accumulation factors in plants. [46, 49-52]

Geographical differences in PFAA concentrations between two regions or sampling sites within one region were highly homologue-specific and varied between the food groups (Figure 2c−2f and Figure S1b−S1k). The most pronounced geographical differences were observed for PFBS, PFHxS, PFOS, PFBA, PFPA and PFHxA which were typically 1−2 orders of magnitude higher in samples from Hubei province compared to Zhejiang province. The elevated PFOS, PFHxS and PFBS concentrations in food samples from Hubei province compared to Zhejiang province were somewhat expected, since these substances are currently produced in the area.[15] The elevated concentrations of short-chain PFCAs are also in agreement with previous measurement in river water from this area.[53] In contrast to PFSAs and short-chain PFCAs, the concentrations of C8−C13 PFCAs were comparable between

297 the two provinces (median concentrations in different food categories within a factor
298 of two) and some food categories even showed higher levels for Zhejiang compared
299 to Hubei. This may be explained by fluoropolymer manufacturing facilities located
300 upstream the Qiantang river or industrial use of telomer-based precursors which can
301 be degraded to form long-chain PFCAs. Figure S2a-S2d displays the spatial trends for
302 the different sampling sites in Hubei and Zhejiang respectively. Strong correlations
303 between a large number of PFAAs (Table S9) and decreasing concentrations with
304 increasing distance to the POSF production facility indicate that the production
305 facility was an important point source also for short-chain PFCAs (Figure S2a-S2b).
306 The concurrent emissions of PFCAs from this facility, which primarily produces
307 PFSAs, may be attributed to impurities and/or degradation products from the
308 manufacturing process.[5, 27, 53] However, it is also possible that the production
309 inventory for this particular plant is incomplete and manufacture of additional
310 fluorochemical products may help to explain the high levels of short-chain PFCAs.
311 The lack of a clear spatial trend of PFSAs and PFCAs among sampling sites in
312 Zhejiang (Figure S2c-S2d) indicate that there are no distinct point source within the
313 sampling area.



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315 **Figure 2.** Concentrations of (a) ∑PFSAs, (b) ∑PFCAs, (c) PFBS, (d) PFBA, (e) PFOS, and (f)
316 PFOA in different food categories from Hubei and Zhejiang province respectively. It should
317 be noted that the scales of the y-axis vary for the different PFASs due to the large variability
318 in concentrations.

319

3.2. Total dietary intake of PFAAs

Based on the PFAA concentrations in different food categories and site-specific intake data, EDIs were estimated for the adult population in Hubei and Zhejiang province respectively. As shown in Table 1, the total dietary intake of ∑PFAAs in Hubei province (998 ng kg^{-1} day^{-1}) was more than two orders of magnitude higher than in Zhejiang province (9.03 ng kg^{-1} day^{-1}) in the lower bound scenario. In Hubei province, the largest contribution to the EDI for ∑PFAAs was from PFBA, PFPA, PFHxA and PFOS whereas EDI for ∑PFAAs in Zhejiang province was dominated by PFDcA, PFUnDA, PFTrDA and PFOS. The percentage difference in ∑PFAAs dietary intakes between the upper- and lower bound scenario for Hubei province was 0.3% demonstrating that non-detects had a negligible influence on the EDI calculations. A larger difference between the upper- and lower bound scenario (37.8%) was observed for Zhejiang province indicating that improvements in analytical techniques and detection frequency could reduce the uncertainty in calculated EDIs.

Table 1 Average estimated daily intake (EDI) of PFAA compounds from foods for adults in Hubei and Zhejiang (ng kg^{-1} day^{-1}) [a, b, c, d]

Compounds	EDI for point source in Hubei		EDI for application area in Zhejiang	
	Lower bound ND=0 [e]	Upper bound ND=½ MDL	Lower bound ND=0	Upper bound ND=½ MDL
PFBS	12.2	13.4	0.39	0.46
PFHxS	5.29	5.36	0.01	0.11
PFOS	86.7	87.5	1.66	3.25

PFBA	682.2	682.5	0.21	1.40
PFPA	128.3	128.3	0.08	0.14
PFHxA	76.3	76.4	0.01	0.23
PFHpA	2.94	2.98	0.003	0.08
PFOA	1.15	1.18	0.59	0.71
PFNA	0.45	0.48	0.34	0.39
PFDcA	0.74	0.82	1.83	1.94
PFUnDA	1.05	1.08	1.47	1.53
PFDoDA	0.13	0.17	0.78	0.84
PFTrDA	0.24	0.27	1.05	1.10
PFTeDA	0.01	0.18	0.58	0.81
∑PFAAs	997.9	1001	9.03	14.5

338 [a] EDI calculated for male adults with an assumed average body weight 61kg.

339 [b] Calculations were not performed for PFDcDA and PFOSA due to the low detection
340 frequencies (<3%).

341 [c] Fish liver were not included into the calculation of EDI due to lack of consumption data.

342 [d] The lower bounds (LB) and upper bounds (UB) of average EDIs were calculated by using
343 zero or half the MDL to substitute values of non-detects respectively.

344 [e] ND: not detected.

345 In Figure 3, the relative contribution of different food categories to total dietary
346 intakes are presented. Leafy vegetables were the main source of ∑PFAAs in Hubei
347 province while fish and eggs dominated the dietary intake of ∑PFAAs in Zhejiang
348 province. These differences were primarily due to the geographical difference in

PFAA concentrations (as discussed above), but they also reflect differences in dietary habits between the provinces. For instance, the population in Hubei had a significantly lower consumption of fish and meat and higher consumption of leafy vegetables compared to Zhejiang (Table S6). Despite these differences in consumption habits, the relative importance of different food categories was relatively consistent between the two provinces when considering individual PFAAs. Fish, eggs and offal were the dominating sources of dietary intake for PFOS and C9-C13 PFCAs whereas leafy vegetables or legumes dominated the intake of PFBS and short-chain PFCAs. This demonstrates that while the magnitude of exposure to PFAAs is strongly influenced by local emission sources (as shown in Table 1), the dietary exposure pathways of different PFAAs are primarily governed by the intrinsic chemical properties leading to accumulation in plants and animals respectively (as discussed above). For PFOA and PFHxS there were, however, significant contributions to the total dietary intake from both animal food products (eggs, fish and offal) and plants (leafy vegetables, legumes and cereals) and some differences in the dominating dietary exposure pathway between the two provinces. This can be explained by the fact that these compounds are moderately water soluble and not strongly bioaccumulative in aquatic food chains.[6]

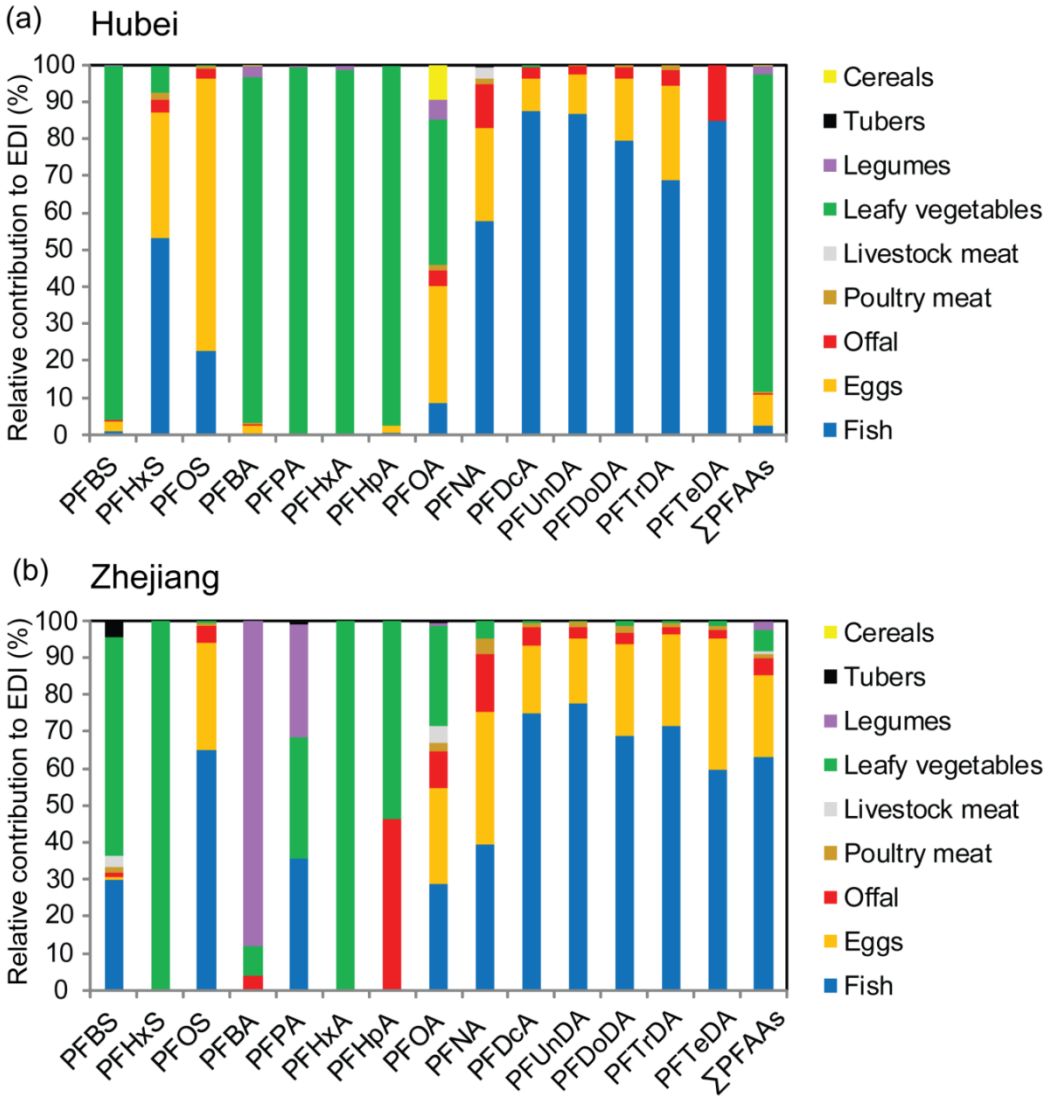

Figure 3. Relative contribution of different food categories to EDIs for different PFAA homologues in samples from (a) Hubei and (b) Zhejiang respectively.

3.3. Comparison with dietary intake assessments from other countries

In order to put the EDIs calculated here into a global perspective a comparison with previous assessments from Europe,[22, 54-57] North America,[58-60] Japan,[61] and Korea[62] is provided in Table S10. Overall, EDIs of ∑PFAAs reported in all previous studies vary between 0.64 − 22.0 ng kg^{-1} day^{-1}. In this context, the EDIs for Hubei province represent highly elevated exposures exceeding previous studies by several

orders of magnitude. The high EDIs in Hubei are consistent with biomonitoring studies reporting the highest serum concentrations of PFOS ever measured in non-occupationally exposed humans from a population of high fish consumers around Tangxun Lake.[10] Collectively, these two studies, which were conducted in different parts of Hubei province, demonstrate that the emissions from ongoing POSF-production in China lead to some of the highest PFAA exposures in the world. Considering that there are currently about 15 enterprises in China producing POSF (the majority in Hubei and Fujian province)[15] studies to assess exposure in these hot spot areas including additional pathways such as drinking water and dust are strongly encouraged. Two previous studies on PFAAs surrounding the same point source in Hubei have shown that PFAAs in tap-water (as drinking water) was not detectable or at very low levels, indicating that PFAAs intake from solid foods may play a more important role of dietary exposure in this region.[27, 63] However, when drinking water is produced by using groundwater, point sources might play a role in the overall exposure.[64] The source of drinking water in relation to the point source is often unclear, making any assumptions challenging. A more detailed approach covering the dietary contribution of drinking water to the Chinese population is needed and was not part of the frame of this project. Also, additional routes of exposure as for example exposure through skin contact and inhalation, due to contact with consumer products and others, as well as the here not discussed exposure via drinking water may also be significant contributors to overall exposure.

The EDIs of ∑PFAAs (LB = 9.03 ng kg^{-1} day^{-1}; UB = 14.5 ng kg^{-1} day^{-1}) from Zhejiang province were also in the higher range of previous studies. When comparing EDIs from different studies it is, however, important to consider the influence of analytical protocols and treatment of non-detects in the data sets. For example, it is likely that EDIs reported in recent studies are more robust as the development of analytical techniques has improved detection frequency, precision, and accuracy of PFAAs in food.[34, 65] EDIs may also be affected by the sample collection method and

calendar year that the study was performed. The standard approach to estimate dietary intake is by collection and analysis of composite foods (sometimes referred to as food basket samples) where a large number of commonly consumed food items are pooled.[56-60] Many studies, including this one, collected and analyzed individual food items which are subsequently aggregated into food categories for calculation of EDIs.[22, 55, 62] A third approach, which is used more seldom, is the duplicate diet method where duplicate food portions consumed by one individual during one day is pooled and analyzed as a homogenate.[54, 61] When comparing our results with Klenow et al.,[55] who applied similar food sampling strategy, analytical approach and EDI calculations as in this study, the lower bound EDIs in Zhejiang province appear to be approximately an order of magnitude higher than those in Europe (LB = 0.58 ng kg^{-1} day^{-1}; UB = 1.14 ng kg^{-1} day^{-1}). This may be an indication of an overall higher EDIs of PFAAs in China compared to other countries. However, due to the methodological aspects mentioned above and large variability between different studies the comparison of EDIs should be interpreted with caution.

3.4 Implications for human health risks of PFAA exposure

The high EDIs in Hubei province also warrants an assessment of the human health risks associated with this exposure. Although, no guidelines for dietary intake of PFAAs exist in China, health-based intake values for PFOS have been established in other parts of the world. The European Food Safety Agency (EFSA) has set the tolerable daily intake (TDI) of PFOS to 150 ng kg^{-1} day^{-1} based on the no observed adverse effect level from a sub-chronic study in cynomolgous monkeys.[66] TDIs of PFOS suggested by the UK Committee on Toxicity of Chemicals in Food and German Federal Institute for Risk Assessment are 300 ng kg^{-1} $day^{-1}$and 100 ng kg^{-1} day^{-1}, respectively.[67, 68] A more recent health advisory from the United States Environmental Protection Agency used substantially lower reference doses (20 ng kg^{-1} day^{-1}) for both PFOA and PFOS derived from developmental effects in rats.[69] Based on these health advisory assessments it can be concluded that the EDIs for

PFOS in Hubei province (87 ng kg^{-1} day^{-1}) are associated with risks for adverse human health effects. A comprehensive analysis on EDIs determined for different age classes in Hubei (Table S11), also show that the EDIs of children (2-14 years of age) are up to two times higher than adults which makes this group particularly susceptible to effects from long-term dietary exposure to PFAAs.

Another important aspect when evaluating human health implications of PFAA exposure for the Hubei population is that there are currently no established TDIs for short-chain PFCAs and PFBS. As these substances contributed to more than 90% of the ∑PFAA EDIs in Hubei province the comparison with advisory guideline for PFOS alone may greatly underestimate the human health risks. In a cumulative risk assessment frame work for 17 per- and polyfluoroalkyl substances developed by Borg et al.[70] it was assumed that PFAA toxicity of short-chain PFAAs can be extrapolated from long-chain homologues based on internal dose (i.e. serum concentrations). By applying this assumption to the exposure situation in Hubei province it seems likely that the high EDIs of short-chain PFAAs would contribute to the cumulative health risks of PFAAs despite a more rapid elimination than PFOS.[10] So far, the low bioaccumulation potential in fish and more rapid urinary clearance of short-chain PFAAs in humans has been the main reasons for the fluorochemical industry to promote this group of chemicals as safe substitutes.[12] This study, however, demonstrates that accumulation in plants and subsequent dietary exposure are important mechanisms that need to be considered for accurate risk assessment of short-chain PFAAs.

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