Levels and profiles of long-chain perfluorinated carboxylic acids in human breast milk and infant formulas in East Asia

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Abstract

In this study, 90 human breast milk samples collected from Japan, Korea, and China were analyzed for perfluorooctanoic acid (PFOA) (C8), perfluorononanoic acid (PFNA) (C9), perfluorodecanoic acid (PFDA) (C10), perfluoroundecanoic acid (PFUnDA) (C11), perfluorododecanoic acid (PFDoDA) (C12), and perfluorotridecanoic acid (PFTrDA) (C13). In addition, infant formulas (n=9) obtained from retail stores in China and Japan were analyzed. PFOA was the predominant compound and was detected in more than 60% of samples in all three countries. The PFOA, PFNA, PFDA, and PFUnDA levels in Japan were significantly higher than those in Korea and China (p<0.05). The PFTrDA level was highest in Korea (p<0.05). The median PFOA concentrations were 89 pg mL^{-1} (48% of total perfluorinated carboxylic acids (PFCAs) (C8–C13)) in Japan, 62 pg mL^{-1} (54%) in Korea, and 51 pg mL^{-1} (61%) in China. The remaining ΣPFCAs (C9–C13) were 95 pg mL^{-1} in Japan, 52 pg mL^{-1} in Korea, and 33 pg mL^{-1} in China. Among the long-chain PFCAs, odd-numbered PFCAs were more frequently detected than even-numbered PFCAs, except for PFDA in Japan. There were no evident correlations between the mother's demographic factors and the PFCA concentrations. PFOA, PFNA, and PFDA were frequently detected in both Japan and China, but there were no significant differences between the two countries. The total PFCA concentrations in the infant formulas were lower than those in the breast milk samples in Japan (p<0.05), but not in China (p>0.05). In conclusion, various PFCAs were detected in human breast

milk samples from East Asian countries. Further studies are needed to evaluate the exposure to long-chain PFCAs and the health risks in infants.

Keywords:

Human breast milk; perfluorinated carboxylic acids; Japan; Korea; China; Asia

1. Introduction

Perfluorinated compounds (PFCs) comprise a large group of man-made fluorinated organic chemicals. They have been produced since the 1950s and are used for various industrial and consumer-related applications, such as food packaging materials, protective coatings for textiles, carpets, papers, and surfactants (Key et al., 1997). During the last decade, PFCs such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been found at considerable levels in various biota samples including the liver and tissues, and especially human blood and serum, worldwide (Fromme et al., 2009).

The toxic effects of PFOS and PFOA have been investigated in animal studies. Prenatal as well as postnatal toxic effects of PFOA and PFOS were observed in rats and mice, including increased liver weights, growth lags, and delayed development. The reproductive and developmental toxicities of these chemicals toward humans are of particular concern (Lau et al., 2004). Several epidemiological investigations have raised concerns regarding the developmental effects of PFOS and PFOA on children, such as low birth weights (Steenland et al., 2010).

In the Stockholm Convention on Persistent Organic Pollutants, PFOS is listed in Annex B (Wang et al., 2009). Fluoropolymer manufacturers have also committed themselves to voluntarily reducing PFOA emissions under a stewardship program by the US EPA (EPA, 2006). The temporal trends in serum levels have revealed decreases in the serum levels of both PFOA and

PFOS in the United States, Norway, and Japan since 2000 (Olsen et al., 2007; Harada and Koizumi, 2009; Haug et al., 2009; Harada et al., 2010).

In contrast to PFOS and PFOA, little information is available for perfluorinated carboxylic acids (PFCAs) with longer chains than PFOA. The emissions of perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUnDA) were 25 and 7 metric tons, respectively, in 2000 (Prevedouros et al., 2006). A modeling study indicated that these PFCAs could also have been emitted from precursor compounds, such as fluorotelomer alcohols (FTOHs), for decades (Van Zelm et al., 2008). Recent evidence suggests that the toxicological effects of PFCAs are strongly correlated with their chain lengths and functional groups (Upham et al., 1998; Matsubara et al., 2006; Wolf et al., 2008; Liao et al., 2009). Therefore, the effects of exposure to long-chain PFCAs need to be clarified, especially in infants.

Human breast milk and infant formulas are considered to be the main PFC exposure sources for infants during the lactation period. Indeed, contamination of PFCs in human breast milk has been reported in various studies from Asia (So et al., 2006; Tao et al., 2008; Nakata et al., 2009; Liu et al., 2010; Kim et al., 2011; Liu et al., 2011), the United States (Kuklenyik et al., 2004; Tao et al., 2008; von Ehrenstein et al., 2009), and Europe (Karrman et al., 2007; Bernsmann and Furst, 2008). However, the available data for PFCAs with longer chains than PFNA in human breast milk are limited, because of the low recoveries of long-chain PFCAs from human breast milk samples (Karrman et al., 2007).

The aim of the present study was to investigate the current levels of long-chain PFCAs in human breast milk in East Asian countries, which were reported to show increasing trends for long-chain PFCAs in serum (Harada et al., 2011). Human breast milk samples collected from Japan, Korea, and China were analyzed for PFOA, PFNA, perfluorodecanoic acid (PFDA), PFUnDA, perfluorododecanoic acid (PFDoDA), and perfluorotridecanoic acid (PFTrDA) using an ion-pair extraction method (Hansen et al., 2001) with modifications. In addition, infant formulas from representative manufacturers in the Japanese and Chinese markets were analyzed for comparison with the PFCA concentrations in the breast milk samples from the same regions.

2. Methods and Materials

2.1. Study population and sample information

To evaluate the geographical differences in the PFCA levels in human breast milk, we selected 30 samples each from Japan, Korea, and China that were stored in the Human Specimen Bank of Kyoto University (Koizumi et al., 2005; Koizumi et al., 2009). For infant formulas, we obtained five products from five different companies in the Japanese market and four products from four different companies in the Chinese market. The main ingredients of these infant formulas were cow milk, cow milk-related products (milk whey protein, lactose, and casein), and edible oils (palm olein and soybean oil). A summary of the sample information is provided in Table

1.

Written informed consent was obtained from all the participants. The research protocol for the present study was reviewed and approved by the Ethics Committee of the Kyoto University Graduate School of Medicine on 14 November 2003 (E25).

2.2. Standards and reagents

Analytical standards for the PFCAs, $^{13}C_4$-labeled PFOA and $^{13}C_5$-labeled PFNA, were obtained from Wellington Laboratories (PFC-MXA, MPFOA, and MPFNA; Guelph, Ontario, Canada).

Methanol, acetone, dichloromethane (DCM), and hexane (purity: >99%, pesticide analysis grade) were obtained from Kanto Chemicals (Tokyo, Japan). Ethyl acetate (pesticide analysis grade), methyl *t*-butyl ether (MTBE, pesticide analysis grade), tetrabutylammonium hydrogen sulfate (TBA), sodium carbonate, sodium bicarbonate, and benzyl bromide were purchased from Wako Pure Chemicals (Osaka, Japan). Ultrapure water (Milli-Q™ Reference; Millipore, Billerica, MA) was used for all solutions. MTBE, DCM, and hexane were prefiltered through silica gel (Presep-C silica gel; Wako Pure Chemicals). Methanol, ethyl acetate, and acetone were distilled before use. Milli-Q water was filtered through an Oasis WAX column (Waters, Milford, MA).

140 *2.3. Sample preparation and extraction*

141 Frozen human breast milk samples were thawed and returned to room
142 temperature before extraction. A liquid–liquid and solid–phase extraction
143 method was used to extract the PFCAs in the samples. Aliquots of breast
144 milk (2 mL) together with an internal standard ($^{13}C_4$-PFOA, 1 ng) were
145 placed in 15-mL polypropylene sample tubes. Next, 2 mL of 0.5 M TBA/0.25
146 M sodium carbonate buffer (pH adjusted to 10 using NaOH) and 2 mL of
147 methanol were added to the samples and vortexed for 15 s. After addition of
148 3 mL of MTBE, the samples were mixed again and centrifuged at 10,000 rpm
149 for 5 min. The supernatants were separated into new glass tubes. Another 3
150 mL of MTBE was added and the extraction was performed again. The
151 combined sample extracts were dried under a gentle stream of nitrogen.
152 Subsequently, each extract was dissolved in 4 mL of 1:1 MTBE/DCM and
153 loaded onto a Presep-C silica gel column preconditioned with 45 mL of
154 methanol and 4 mL of 1:1 MTBE/DCM on a vacuum manifold. The silica gel
155 column was washed with 10 mL of hexane and 30 mL of ethyl acetate that
156 had been prefiltered through another Presep-C silica gel column. The target
157 fraction was eluted using 12 mL of acetone that had been prefiltered through
158 an alumina column (Sep-Pak plus alumina N; Waters). The eluate was dried
159 under a gentle stream of dry nitrogen. The residue was then redissolved in
160 100 μL of 0.1 M benzyl bromide/acetone solution and derivatized at 60 °C for
161 1 h. No further clean-up was conducted.

162 The infant formulas were dissolved in Milli-Q water according to the

guidelines on the packages. Cow milk (4 mL), Milli-Q water (2 mL, procedural blank), and infant formulas (2 mL) were treated by the same procedure used for the human breast milk samples.

2.4. Instrumental analysis

The extracts were analyzed by gas chromatography–mass spectrometry (Agilent 6890GC/5973MSD; Agilent Technologies Japan Ltd., Tokyo, Japan) in the electron impact ionization mode. The PFCAs were separated on a J&W DB-5MS column with a helium carrier gas (1.5 mL min^{-1}). The splitless injection volume was 2 µL. The oven temperature was 70 °C for 2 min initially, and then ramped up to 280 °C at 20 °C min^{-1}. The monitored ions are listed in Table 2. Standard stock solutions (2 µg mL^{-1}) were diluted to seven working standard solutions (4, 2, 1, 0.8, 0.4, 0.2, and 0.1 ng mL^{-1}) by serial dilutions in acetone. All the standard solutions were stored in a refrigerator at 4 ± 2 °C for a maximum period of 3 months from the date of preparation.

The instrumental detection limits (IDLs) were defined as the mass of analyte producing a peak with a signal–to–noise ratio of 3, and ranged from 0.5 pg (PFUnDA, PFDoDA, and PFTrDA) to 0.2 pg (other PFCAs).

2.5. Quality assurance

We used Milli-Q water as the procedural blank control. The average blank values (n=6) were 20.5 pg mL^{-1} (PFOA), 5.2 pg mL^{-1} (PFNA), and 7.1 pg mL^{-1}

(PFDA). In the case of blank levels, the mean blank signal was subtracted from the calculated sample concentration only if the calculated sample concentration was three times higher than the blank concentration. If no signal was detected in the blank samples, the method detection limits (MDLs) were based on the IDLs and 2-mL milk samples. Using this method, we established that the MDLs ranged from 40 to 10 pg mL^{-1} (Table 2).

$^{13}C_4$-PFOA was used as an internal standard for the PFCAs. $^{13}C_5$-PFNA was used to monitor the recovery of the internal standard. The recoveries of the PFCAs were examined by spiking 500 pg of each standard compound into cow milk. The mean recoveries of PFOA, PFNA, PFDA, PFUnDA, PFDoDA, and PFTrDA were 104%, 84%, 109%, 95%, 92%, and 97%, respectively. Typical chromatograms of PFCAs obtained in this study are shown in Supplemental figure 1.

For quality assurance and quality control of our analytical methods and procedures in the analysis of PFCAs in the breast milk samples, we measured PFCAs in standard reference materials from the National Institute of Standards and Technology (Table 2). The PFCA values were comparable to those reported previously (Keller et al., 2010).

2.6. Statistical analysis

We calculated the percentages of detection of the PFCAs in each country, and determined the range, median, mean, standard deviation, geometric mean, and 90th percentile concentration. Concentrations below the MDL

were replaced by half of the MDL for statistical analyses. Nonparametric statistical tests were applied to assess the statistical significance of differences between values. The Steel–Dwass test was used to compare differences in the PFCA concentrations among different countries after the Kruskal–Wallis test. Spearman's rank correlation analysis was used to examine the relationships between the PFCA levels and the mother's age and child's birth weight. The Mann–Whitney test was used to examine the relationships between the PFCA levels and alcohol drinking and cigarette smoking. The level of statistical significance was set at $p<0.05$. A factor analysis was used to elucidate the number of potential factors of sources. The analyses were conducted via a correlation matrix. Eigenvectors were employed for the analysis when the eigenvalues were greater than 1. Normalized varimax rotation was applied to these eigenvectors. The statistical analyses were carried out using the software JMP® 4 (SAS Institute Inc., Cary, NC) or R Ver. 2.12.1. (Ihaka and Gentleman, 1996) for the Steel–Dwass test.

3. Results

3.1. PFCA concentrations in breast milk in Japan, Korea, and China

The demographic characteristics of the participants are shown in Table 1. The participants in Korea were, on average, about 3 years older than those in Japan and China. The descriptive statistical data are summarized in Table 3. PFOA was the predominant compound and was detected in more

than 60% of samples in all three Asian countries. The median concentration of PFOA ranged from 51 pg mL^{-1} in China to 89 pg mL^{-1} in Japan. The PFOA levels in Japan were significantly higher than those in Korea and China (p<0.05, Steel–Dwass test).

PFNA and PFUnDA were detected at comparable rates to PFOA in the three countries. The levels of PFNA and PFUnDA were higher in Japan than in Korea and China (p<0.05, Steel–Dwass test). PFDA was frequently detected in Japan (67%), but rarely detected in Korea (13%) and China (13%). In Korea, half of the milk samples contained detectable levels of PFTrDA, which was the highest among the three countries (p<0.05, Steel–Dwass test). PFDoDA was detected in few samples in the three Asian countries and there were no significant differences (p>0.05). Regarding the total PFCAs in the milk samples, PFOA accounted for 48%, 54%, and 61% in Japan, Korea, and China, respectively. Among the long-chain PFCAs, odd-numbered PFCAs were more frequently detected than even-numbered PFCAs, except for PFDA in Japan.

PFOA was only significantly correlated with PFNA (ρ coefficient: >0.4) (Supplemental table 1). There were also significant correlations between PFNA and PFUnDA, PFDA and PFUnDA, and PFUnDA and PFTrDA (ρ coefficients: >0.4). In general, the PFCA concentrations showed strong correlations between PFCAs of similar (i.e. adjacent) chain lengths.

The factor analysis revealed that two potential factors, F1 and F2, accounted for 43.3% and 19.0% of the total variance (with eigenvalues of >1),

255 respectively (Table 4). After varimax rotation, F1 indicated higher
256 eigenvectors for PFOA, PFNA, PFDA, and PFUnDA, while F2 had positive
257 eigenvectors for PFUnDA and PFTrDA. The mean factor scores of each
258 sampling site are also shown in Table 4. Although the F1 score was higher in
259 Kyoto than in the other two sites (p<0.05, Steel–Dwass test), there were no
260 significant differences in the F2 scores among all the sampling sites (p>0.05,
261 Kruskal–Wallis test).
262
263 *3.2. PFCA concentrations in commercially available infant formulas in Japan*
264 *and China*
265 The PFCA concentrations in the infant formulas are shown in Table 5.
266 PFOA, PFNA, and PFDA were frequently detected in both Japan and China,
267 but there were no significant differences between the two countries.
268 PFUnDA was detected at 40.7 pg mL^{-1} in one sample in Japan. PFDoDA and
269 PFTrDA were not detected in any of the formula samples. Compared with the
270 breast milk samples, the PFOA levels were 4-fold and 2-fold lower in the
271 formula samples in Japan and China, respectively. The total PFCA
272 concentrations in the infant formulas were lower than those in the breast
273 milk samples in Japan (p<0.05, Kruskal–Wallis test), but not in China
274 (p>0.05, Kruskal–Wallis test).
275
276 *3.3. Relationships between the PFCA levels and the participants'*
277 *characteristics*

278 To evaluate the influence of the participants' characteristics on the PFCA
279 concentrations in the human breast milk samples, Spearman's correlation
280 analyses were performed (Supplemental table 2). PFDoDA was positively
281 correlated with the mother's age in Korea (p<0.05) and PFNA was negatively
282 correlated the mother's age in China (p<0.05). However, these correlations
283 were not consistent among the three countries. In several epidemiological
284 studies (Steenland et al., 2010), the PFC concentrations in the cord blood or
285 maternal pregnancy serum were reported to be associated with the child
286 birth weight. In our study subjects, the correlations between the PFCA
287 concentrations and the child birth weights were not significant. The lactation
288 period was also examined for correlations with PFCAs in the milk samples.
289 PFDA was correlated with the lactation period in Japan (p<0.05), but not in
290 Korea. Among the PFCAs, there were no clear trends in the correlation
291 coefficients. Although consumption of fish was one of the sources of exposure
292 to PFCAs, no significant associations were observed between the PFCA
293 levels in the milk samples and the fish intake (p>0.05). Non-smoking
294 mothers in Japan had relatively higher PFCAs levels than other mothers,
295 but the difference was not significant (p>0.05). The PFCA levels in the milk
296 samples were compared between non-drinking mothers and other mothers.
297 The PFTrDA and PFNA levels were lower in non-drinking mothers in Japan
298 and Korea (p<0.05, Mann–Whitney test).
299
300 *3.4. Daily intake estimation and hazard assessment for infants*

The tolerable daily intake (TDI) for PFOA was established to be 1500 ng kg body weight^{-1} d^{-1} by the Scientific Panel on Contaminants in the Food Chain requested by the European Food Safety Authority in 2008 (). The average breast milk consumption rate and body weight for 1-year-old infants were assumed to be 600 g d^{-1} and 7.3 kg, respectively (Schecter, 1994). Based on these assumptions, the daily intakes of PFCAs by 1-year-old infants were estimated (Supplemental table 3). For the infant formulas, the calculated mean levels were only 0.1–0.2% of the TDI. Meanwhile, the calculated levels for the human breast milk samples (means: 0.3–0.5% of the TDI; 90th percentiles: 0.6–0.9% of the TDI) were higher than those for the infant formulas. As of 2011, there is no established TDI for PFCAs that are longer than PFOA.

4. Discussion

In the present study, we first demonstrated contamination of human breast milk with PFDoDA and PFTrDA in Asian countries. Simultaneously, we confirmed similar long-chain PFCA profiles in East Asian breast milk samples, as previously reported (Liu et al., 2010; Kim et al., 2011; Liu et al., 2011). A characteristic PFCA composition was observed for PFUnDA and PFTrDA (both odd-numbered PFCAs) with residual PFDoDA and PFDA (both even-numbered PFCAs). These findings indicated that odd-numbered PFCAs predominated over even-numbered PFCAs in East Asian breast milk samples. The PFCAs with longer chains than PFOA reached 47% of the total

PFCAs for the average of the three countries. This finding suggests that infants are exposed to not only classical PFOA but also long-chain PFCAs in East Asia. Indeed, a factor analysis demonstrated two potential factors, F1 and F2, as sources of PFCAs. F1 had loading on medium-chain PFCAs, of which the factor score was significantly higher in Kyoto than in Beijing or Seoul. Kyoto is located in the Hanshin area, where there is a large emission source of PFOA and its related by-products (Niisoe et al., 2010). Thus, F1 may represent a local emission source of PFCAs. On the other hand, F2 had strong associations with long-chain PFCAs. The factor scores for F2 in the three large cities did not differ, suggesting that there are similar sources of long-chain PFCAs (>C10) in the three counties. Therefore, PFCA (C10–C13) exposure through the breast milk is likely to commonly occur in East Asian countries. We are the first to document this possibility.

The sources of long-chain PFCAs are still unknown. Odd-numbered PFCAs predominated in the PFCAs in this study. As previously reported (Harada et al., 2011), odd-numbered PFCAs also predominated in serum samples collected from Asian women. A review by Prevedouros et al. (2006) indicated that odd-numbered PFCAs have been manufactured in Japan via oxidation of fluorotelomer olefins. Industrial application of these odd-numbered PFCAs might contribute to the pattern of PFCAs in breast milk samples collected from East Asian women. Although FTOHs are possible precursors of PFCAs, biodegradation of FTOHs preferentially yields even-numbered PFCAs (Fasanoa et al., 2009). Therefore, FTOHs are unlikely to be the main

exposure source for Asian populations. Further investigations into the sources and exposure routes are needed to predict the future trajectory of these PFCA levels.

Although data concerning the PFC levels in human breast milk are not as abundant as those in blood samples, we can still find several reports for PFCs in human breast milk from Asia, the United States, and Europe. The related data are summarized in Table 6. In Japan, the PFOA levels in three regions were comparable (Tao et al., 2008; Nakata et al., 2009). In Korea, PFOA had a higher value in the present study compared with earlier research in Seoul (Kim et al., 2011) (mean: 63.8 *vs.* 41 pg mL^{-1}, range: 14.7–172.1 *vs.* 21–77 pg mL^{-1}). This increase may be consistent with the increasing trend in the PFOA level in serum samples by 1.27-fold from 2000 to 2007 in Korea (Harada et al., 2010).

In China, the concentrations of PFOA in Zhoushan ranged from 47 to 210 pg mL^{-1} (So et al., 2006) and in 12 different provinces of China, the mean PFOA level was 116 pg mL^{-1} (Liu et al., 2010). The PFOA levels showed large variations within China, although the other PFCAs were comparable among two previous studies and this study. In Southeast Asian developing countries, most of the milk samples did not contain detectable PFCAs (Tao et al., 2008), which might result from differences in industrialization. In the United States and European countries, PFOA and PFNA were detected in human breast milk samples, but long-chain PFCAs were not observed (Kuklenyik et al., 2004; Karrman et al., 2007; Bernsmann and Furst, 2008; Tao et al., 2008;

370 Volkel et al., 2008; Karrman et al., 2010; Llorca et al., 2010). The occurrence
371 of long-chain PFCAs in East Asian countries is likely to be a fingerprint of
372 the sources of exposure.

373 Infant formulas were also evaluated in this study. The compositions of
374 PFCAs in the infant formulas were different from those in the breast milk
375 samples. In Japan, the levels of PFCAs in the infant formulas were lower
376 than those in the breast milk samples. These findings probably reflect
377 differences in the bioaccumulation potential between humans and cows.

378 In our study, we found no evident relationships between the mother's
379 characteristics and the PFCA concentrations. Although there were
380 statistically significant differences for some of the PFCAs, no consistent
381 trends were observed among the three countries.

382 The estimated daily intakes of PFOA were much lower than the TDI in
383 this study. These observations may indicate that the health risks for PFOA
384 intake from breast milk and infant formulas are limited. However, infants
385 have different susceptibilities to adults with regard to their dynamic growth
386 and developmental processes (Sly et al., 2008). In addition, the toxicokinetics
387 and toxicities of long-chain PFCAs are still unclear, although these PFCAs
388 comprised 48% of the total PFCAs in this study. These uncertainties
389 necessitate more comprehensive toxicological studies on long-chain PFCAs,
390 including PFOA.

391 The limitations of this study are the sample sizes and the sample selection
392 method. It should be noted that these findings were based on a relatively

small number of non-randomly selected volunteer samples. Moreover, the sampling times for the Chinese donors were uncertain, although it is known that the profiles of chemicals may change during the lactation period. Considering these limitations, a future extended study is required for confirmation of these findings,

In conclusion, various PFCAs were detected in human breast milk samples from East Asian countries. Further studies are needed to evaluate the exposure to long-chain PFCAs and the health risks in infants.

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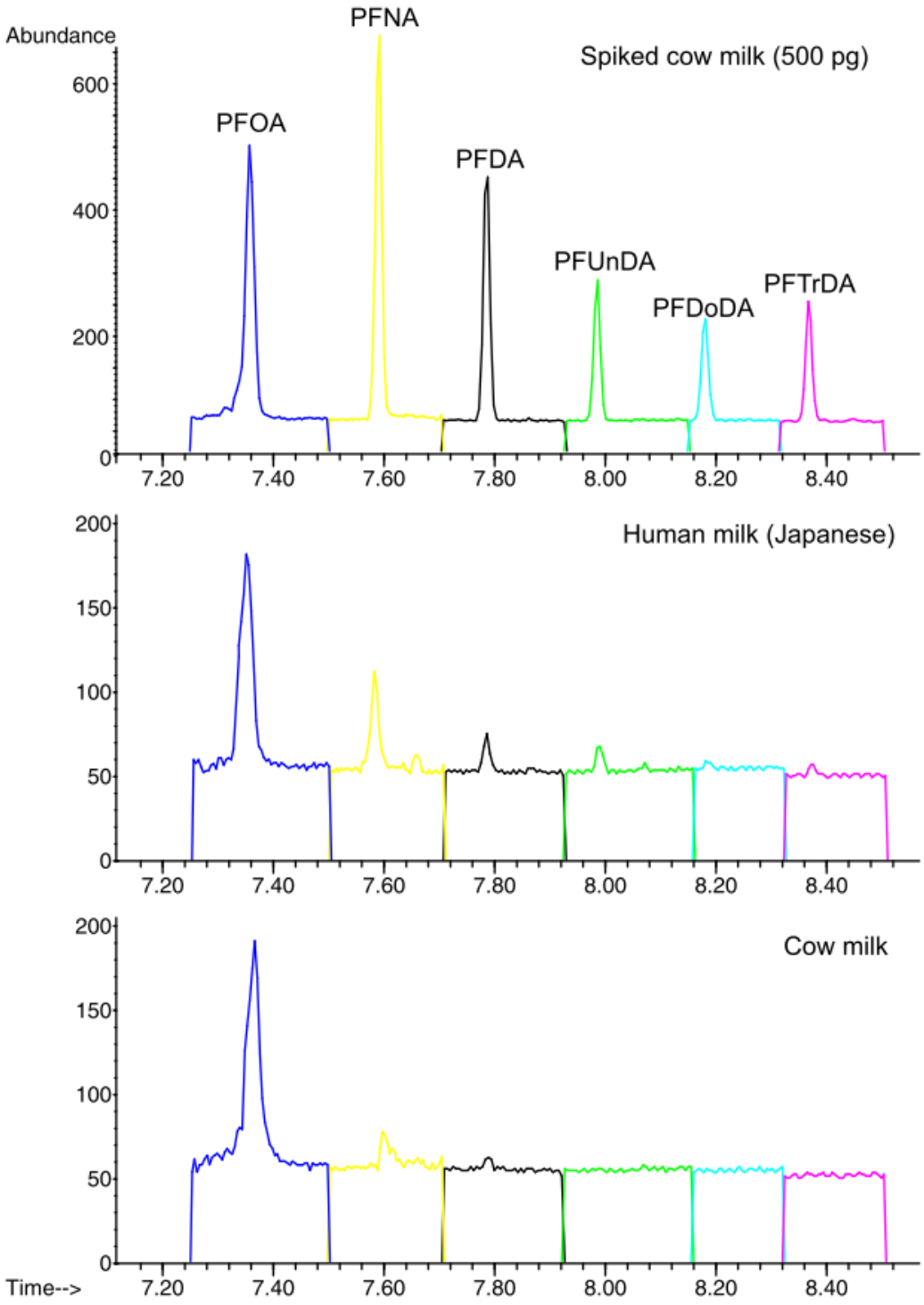

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545 Supplemental figure 1.

546 Typical chromatograms of PFCAs obtained in this study.

Table 1
Study areas and sample information.

a. Human milk

Sampling site	*n*	Year	Age (year)[a]	(range)	Parity(*n*)	Smoking[bc]	Drinking[c]	Lactation period (week)[a]
Japan								
Kyoto	30	2010	27.8±3.4	(21-33)	1(30)	Ex (7), non (23)	Ex(18), non(12)	3.0±0.5
Korea								
Seoul	30	2010	30.9±2.3	(26-36)	1(22), 2(8)	Ex (3), non (27)	Curr(3), ex(2), non(25)	1.6±1.1
China								
Beijing	30	2008, 2009	27.0±1.7	(23-30)	1(30)	Non (30)	Curr(2), ex(27), non(1)	NA

b. Infant formula

Sampling site	*n*	Year	Targeted infant age (month)
Japan			
Kyoto	5	2010	0-12
China			
Beijing	4	2010	0-12

[a]Data are presented as the mean ± standard deviation.
[b]Including second-hand tobacco smoke.
[c]Curr: current; ex: experienced; non: never.

Table 2
Recoveries and detection limits for the PFCA analyses in human serum samples.

Compound	Quantification (confirmation)	Instrument detection limit[a] (pg)	Blank (pg mL^{-1}) range (mean)	Method detection limit[b] (pg mL^{-1})	Recovery and (reproducibility) mean percentage (SD) (*n* =9)	Standard Reference Material 1954[c]		
						This study (pg g^{-}	U. Toronto[d] (pg g^{-1})	Env. Canada[d] (pg g^{-1})
PFOA	504 (485)	0.2	12.0-32.1(20.5)	40	104(14)	117	149	116
$^{13}C_4$ PFOA	508 (489)	-	-	-	99(12)	-	-	-
PFNA	554 (535)	0.2	<5-14.7(5.2)	10	84 (44)	24	22	<16
$^{13}C_5$ PFNA	559 (540)	-	-	-	-	-	-	-
PFDA	604 (585)	0.2	<5-25.8(7.1)	15	109 (32)	16	14	<6
PFUnDA	654 (635)	0.5	<10	10	95 (45)	12	7	<14
PFDoDA	704 (685)	0.5	<10	10	92 (25)	<10	3	<8
PFTrDA	754 (735)	0.5	<10	10	97 (27)	<10	-	-

[a]Injection of 2 µL.
[b]Milk sample of 2 mL (the mean blank signal was subtracted from the calculated sample concentration only if the calculated sample concentration was three times higher than the blank concentration).
[c]Milk standard reference material from the National Institute of Standards and Technology, 1954.
[d]Analyzed by the University of Toronto and Environment Canada (Keller et al., 2010).

Table 3
Concentrations of PFCAs in breast milk samples.

Sampling site		Concentration (pg mL^{-1}) PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA	ΣPFCAs
Japan	*n* >MDL(%)	28(93.3)	27(90.0)	20(66.7)	28(93.3)	5(16.7)	10(33.3)	30(100.0)
Kyoto	Median	89(<40-194)A*	31(<10-72)A*	17(<15-65)A*	35(<10-100)A*	<10(<10-29)n.s.	<10(<10-91)AB*	184(50.3-413.5)A*
	Mean	93.5±43.7	32.1±17.2	21.3±15.0	36.6±21.8	<10	15.2±20.6	194.5±83.6
	GM(GSD)	82.7(1.7)	26.5(2.0)	16.9(2.0)	30.4(2.0)	<10	<10	176.7(1.6)
	P90	173	62	44	65	22	36	315
Korea	*n* >MDL(%)	24(80.0)	20(66.7)	4(13.3)	22(73.3)	4(13.3)	15(50.0)	28(93.3)
Seoul	Median	62(<40-173)B*	15(<10-41)B*	<15(<15-19)B*	19(<10-51)B*	<10(<10-41)n.s.	10(<10-43)A*	114(<10-283.9)B*
	Mean	64.5±33.7	14.7±9.3	<15	19.6±13.1	<10	16.8±13.5	118.8±50.9
	GM(GSD)	55.5(1.8)	11.9(2.0)	<15	15.3(2.2)	<10	11.7(2.4)	109.7(1.5)
	P90	106	29	15	42	11	40	189
China	*n* >MDL(%)	19(63.3)	21(70.0)	4(13.3)	17(56.7)	3(10.0)	7(23.3)	28(93.3)
Beijing	Median	51(<40-122)B*	15(<10-47)B*	<15(<15-29)B*	15(<10-47)B*	<10(<10-25)n.s.	<10(<10-43)B*	84(<10-200.8)B*
	Mean	51.6±30.6	15.3±9.6	<15	16.0±12.9	<10	<10	87.8±54.9
	GM(GSD)	43.0(1.9)	12.6(2.0)	<15	11.7(2.3)	<10	<10	68.8(2.2)
	P90	103	27	18	42	10	22	164

MDL: method detection limit; GM: geometric mean; GSD: geometric standard deviation; P90: 90th percentile.

*Medians among different sites differ significantly (p <0.05, Steel–Dwass test). For example, the letters A and B indicate that the corresponding values differ significantly at p <0.05, while A and A or B and B indicate that the corresponding values do not differ significantly.

Table 4

Factor analysis among PFCAs.

	Initial solution		Varimax rotated	
	F1	F2	F1	F2
Eigenvalue	2.60	1.14		
Cumulative contribution (%)	43.3	62.3		
Eigenvector				
PFOA	0.387	-0.511	**0.818**	-0.135
PFNA	0.472	-0.375	**0.857**	0.060
PFDA	0.480	-0.020	**0.668**	0.390
PFUnDA	0.518	0.261	**0.563**	**0.677**
PFDoDA	0.114	0.430	-0.086	0.488
PFTrDA	0.340	0.587	0.135	**0.822**
Factor score (mean±SD)*				
		Beijing	-0.5 ± 0.6^{B}	-0.2 ± 0.7
		Kyoto	0.9 ± 1.1^{A}	0.2 ± 1.4
		Seoul	-0.4 ± 0.6^{B}	0.1 ± 0.8

*Means among countries differ significantly (p <0.05, Steel–Dwass test). For example, the letters A and B indicate that the corresponding values differ significantly at p <0.05, while A and A or B and B indicate that the corresponding values do not differ significantly.

Table 5
Concentrations of PFCAs in infant formulas.

Sampling site	Sample no.	Concentration (pg mL^{-1})[a]						
		PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA	ΣPFCAs
Japan	1	<20	<5	<7	<5	<5	<5	<5
	2	35.8	27.0	<7	<5	<5	<5	62.8
	3	30.8	8.0	12.1	<5	<5	<5	50.9
	4	<20	8.6	11.5	<5	<5	<5	20.1
	5	22.5	92.0	19.8	40.7	<5	<5	175.0
	Mean±SD	21.8±11.8	27.6±37.2	10.1±6.9	10.1±17.1	<5	<5	66.4±65.6
China	1	35.4	50.4	14.0	<5	<5	<5	99.7
	2	<20	15.2	<7	<5	<5	<5	15.2
	3	37.1	12.2	12.9	<5	<5	<5	62.2
	4	29.9	11.6	13.9	<5	<5	<5	55.4
	Mean±SD	28.1±12.4	22.4±18.8	11.1±5.1	<5	<5	<5	61.5±29.3

[a]A 4-mL aliquot of each infant formula was analyzed.

Table 6

Comparisons of the PFCA concentrations in human breast milk with reported data (pg ml^{-1}).

Country	Region	Year	*n*		PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA	Reference
Japan	Kyoto	2010	30	Mean	93.5	32.1	21.3	36.6	<10	15.2	This study
				Range	<40-194	<10-72	<15-65	<10-100	<10-29	<10-91	
	Hokkaido	NA	51	Mean	89	35					Nakata et al., 2009
				Range	<12-339	<4-150					
	Ehime	1999	24	Mean	77.7						Tao et al., 2008
				Range	<42.5-170	<8.82-23.9					
Korea	Seoul	2010	30	Mean	64.5	14.7	<15	19.6	<10	16.8	This study
				Range	<40-173	<10-41	<15-19	<10-51	<10-41	<10-43	
		2007	17	Mean	41						Kim et al., 2011
				Range	<43-77	<8.8	<18	<24	<13		
China	Beijing	2008-2009	30	Mean	51.6	15.3	<15	16.0	<10	<10	This study
				Range	<40-122	<10-47	<15-29	<10-47	<10-25	<10-43	
	Zhoushan	2004	19	Mean	106.3	18.1	7.2	19.1			So et al., 2006
				Range	47-210	6.3-62	3.8-15	7.6-56			
	12 provinces	2007	1237	Mean	116.0	16.2	9.9	37.6			Liu et al., 2010
				Range	<14.15-814	6-76	<1.44-63	<1.30-196			
				(24 pooled samples)							
Vietnam	Hanoi, Ho Chi Minh	2000, 2001	40	Range	<42.5-89.2	<8.82-10.9					Tao et al., 2008
Cambodia	Phnom Penh	2000	24	Range	<42.5-132	<8.82-12.3					Tao et al., 2008
Philippines	Quezon	2000, 2004	24	Range	<42.5-183	<8.82-25.0					Tao et al. , 2008
Malaysia	Penang	2003	13	Range	<42.5-90.4	<8.82-14.9					Tao et al., 2008
Indonesia	Jakarta, Purwakarta	2001	20	Range	<42.5	<8.82-135					Tao et al., 2008
India	Chidambaram, Kolkata, Chennai	2002, 2004, 2005	39	Range	<42.5-335	<8.82					Tao et al., 2008
USA	Unknown	2003	2	Range	<200						Kuklenyik et al., 2004
	Massachusetts	2004	45	Mean	43.8	7.26					Tao et al., 2008
				Range	<30.1-161	<5.2-18.4					
Sweden	Uppsala	2004	12	Range	< 209–492	< 5–20	<8	<5			Kärrman et al., 2007
		1996-2004	9	Range	<209	<5-28	<8	<5			
				(Pooled annual composite milk sample)							
Germany	NA	2006	38	Range	201-460						Völkel et al., 2008
				(Archived samples+19 fresh samples)							
	North Rhine Westphalian	NA	203	Range	25-610						Bernsmann et al., 2008
Spain	Tarragona	2007	10	Range	<500	<30	<60	<30	<30		Kärrman et al., 2010
	Barcelona	2008	20		<15.2-907	<11.5	<85.5-1095				Llorca et al., 2010

Supplemental Table 1

Correlations between PFCAs with different chain lengths.

Combination		ρ	p value
PFNA	PFOA	**0.418**	<0.001
PFDA	PFOA	0.321	0.002
PFDA	PFNA	0.369	<0.001
PFUnDA	PFOA	0.359	0.001
PFUnDA	PFNA	**0.475**	<0.001
PFUnDA	PFDA	**0.422**	<0.001
PFDoDA	PFOA	-0.007	0.945
PFDoDA	PFNA	0.010	0.923
PFDoDA	PFDA	0.256	0.015
PFDoDA	PFUnDA	0.110	0.304
PFTrDA	PFOA	0.094	0.377
PFTrDA	PFNA	0.082	0.443
PFTrDA	PFDA	0.031	0.769
PFTrDA	PFUnDA	**0.478**	<0.001
PFTrDA	PFDoDA	0.151	0.156

ρ: Spearman's correlation coefficient.

Supplemental Table 2
Associations between the PFCA concentrations and the participants' characteristics.

Variables		PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA
Mother's age (yr)[a]							
Japan		-0.056	0.054	0.014	0.328	0.371	0.384
Korea		0.317	0.092	0.021	0.186	**0.385***	-0.156
China		-0.119	**-0.421***	0.197	-0.297	0.051	-0.208
Child birth weight (g)[a]							
Japan		-0.104	-0.017	0.101	0.174	-0.017	0.107
Korea		-0.058	-0.103	0.043	0.081	-0.081	0.077
China		NA	NA	NA	NA	NA	NA
Lactation period (wk)[a]							
Japan		0.125	0.104	**0.474***	0.315	-0.026	-0.225
Korea		0.088	-0.044	0.181	-0.121	-0.193	-0.107
China		NA	NA	NA	NA	NA	NA
Fish intake (g/wk)[a]							
Japan		-0.223	-0.173	-0.127	-0.135	0.163	0.161
Korea		0.098	0.026	0.314	0.133	0.072	-0.023
China		NA	NA	NA	NA	NA	NA
Smoking[b]							
Japan	Non-smoker (23)	101±45	35±19	24±16	40±24	9±8	17±23
	Others (7)	69±28	23±6	12±7	27±11	5±0	8±6
Drinking[b]							
Japan	Non-drinker (12)	96±51	36±16	21±4	30±15	6±5	6±3
	Others (18)	92±39	30±18	22±4	41±25	9±8	**21±25***
Korea	Non-drinker (25)	61±27	13±8	8±4	19±13	7±7	15±13
	Others (5)	83±58	**26±10****	7±0	22±14	6±3	25±13

*p <0.05, **p <0.005.

[a]For continuous variables, Spearman's correlation analysis was used for evaluations with the PFCA concentrations.
[b]For categorical variables, the means were compared between two groups by the Mann–Whitney test.

Supplemental Table 3
Daily intake estimations and hazard assessment for 1-year-old infants.

Sampling site			Estimated Intake[a] (ng kg body weight^{-1} d^{-1}) PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA	ΣPFCAs
Japan	Breast milk	Mean	7.7	2.6	1.8	3.0	0.4	1.2	16.0
Kyoto		%[b]	0.5%	-	-	-	-	-	-
		P90	14.2	5.1	3.6	5.3	1.8	3.0	25.9
		%[b]	0.9%	-	-	-	-	-	-
	Infant formula	Mean	1.8	2.3	0.8	0.8	0.2	0.2	5.5
		%[b]	0.1%	-	-	-	-	-	-
Korea	Breast milk	Mean	5.3	1.2	0.6	1.6	0.4	1.4	9.8
Seoul		%[b]	0.4%	-	-	-	-	-	-
		P90	8.7	2.4	1.2	3.5	0.9	3.3	15.5
		%[b]	0.6%	-	-	-	-	-	-
China	Breast milk	Mean	4.2	1.3	0.6	1.3	0.4	0.4	7.2
Beijing		%[b]	0.3%	-	-	-	-	-	-
		P90	8.5	2.2	1.5	3.5	0.8	1.8	13.5
		%[b]	0.6%	-	-	-	-	-	-
	Infant formula	Mean	2.3	1.8	0.9	0.2	0.2	0.2	5.1
		%[b]	0.2%	-	-	-	-	-	-

P90: 90th percentile.

[a]The breast milk consumption rate and body weight for 1-year-old infants were assumed to be 600 g d^{-1} and 7.3 kg, respectively (Schecter, 1994).

[b]Percent of the tolerable daily intake (1500 ng kg body weight^{-1} d^{-1}) for PFOA by the Scientific Panel on Contaminants in the Food Chain requested by the European Food Safety Authority in 2008 (EFSA, 2009).