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REVIEW

Environmental and biological monitoring of persistent fluorinated compounds in Japan and their toxicities

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Abstract Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) comprise a class of per- and poly-fluorinated compounds that have been detected in the environment as well as in humans. The aim of this review is to summarize several monitoring studies in Japan and characterize the toxicokinetics of these compounds. We found that the levels of contamination by these compounds had unique patterns in Japan. The levels of PFOA in serum from inhabitants of the Kansai region were higher than those of other regions. The PFOA levels in air and water samples from the Kansai region were also relatively high. The estimated intakes from these routes partly explain the differences in the serum levels. The toxicokinetics of these compounds have been investigated. Serum samples from male participants had significantly higher geometric means for PFOS and PFOA compared to samples from female participants. This sex-related difference was partly simulated by menstrual blood loss. There are large interspecies differences in the excretion pathways of these compounds. The serum clearances of PFOA via urine were 300–1,000-fold lower in humans than in Wistar rats and Japanese macaques. On the other hand, the biliary excretion of these compounds was comparable in rats and humans, and the long half-lives in humans may be attributable to the low levels of urinary excretion and high biliary reabsorption rates. These findings suggest that qualitative differences in the excretion routes exist between humans and other species. For risk assessment of these compounds, further information regarding sources of exposure and their toxicokinetics is needed.

Keywords Perfluorooctanoic acid · Perfluorooctane sulfonate · Distribution in Japan · Toxicokinetics

Introduction

Per- and poly-fluorinated compounds (PFCs), of which representative chemicals include perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), are a class of specialty chemicals used in a variety of applications. PFOS has been used in lubricants, metal plating, coating formulations, fire-fighting foams, oil and water repellents for leather, paper and textiles, and so on [1]. PFOA has various applications similar to PFOS, but has also been used as a processing aid in fluoropolymer manufacture for over 50 years [2]. PFCs exhibit advantageous physical and chemical properties, which include chemical stability, thermal inertness, and low surface energy, among others.

The estimated historical global PFOA production and emission from fluoropolymer manufacture are in the range of 4,400–8,000 and 3,200–6,900 t, respectively [3]. The global production of PFOS fluoride, a precursor of PFOS, from 1985 to 2002 by 3M Company is estimated to have been 13,670 t [4].

In 2002, however, after 50 years of production, 3M Company, one of the largest companies that produced these compounds, phased out their manufacture because of their persistence in the environment [5]. Despite this, several fluoropolymer manufacturers began producing PFOA as a fluoropolymer processing aid [2].

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PFOA and PFOS have been found globally in a variety of living organisms, including humans and wildlife [6, 7]. Many studies have revealed that these compounds have various toxicities toward living organisms, including humans [8–11]. PFOS has been regulated at various levels by governments, including those of the USA [12], Canada [13], and the European Union (EU) [14]. In the Stockholm Convention on Persistent Organic Pollutants (POPs), the third meeting of the POPs review committee decided to recommend PFOS for listing in Annex A or B of the convention [4]. Following the restriction of PFOS marketing in the EU, the issue of whether PFOA should be included in Directive 76/769/EEC has been discussed. The Environmental Protection Agency of the USA launched a stewardship program, and manufacturers have committed to reducing PFOA emissions [15].

Recent studies have revealed a unique situation in Japan, namely that PFOA contamination has progressed more profoundly than PFOS contamination [16, 17]. In agreement with these observations, serum concentrations in Japanese, albeit limited to subpopulations of Japan, are reported to be higher than those in US populations, while the opposite is true for PFOS [18, 19].

The present review has two main aims. First, we review the environmental and biological monitoring of PFOS and PFOA in Japan. Second, we characterize the toxicokinetics of PFOS and PFOA. We have compared data obtained in Japan with those obtained in other countries as required to clarify the unique situation in Japan.

Distributions of PFOA and PFOS in the water environment in Japan

Several studies have reported the concentrations of PFOA and PFOS in surface water in Japan [17, 20–23], and the data are summarized in Table 1.

The geometric mean concentrations of PFOA in five regions were within the range of 1–3 ng/l, except for the Kansai region. In the Kansai region, the PFOA concentrations in surface water were much higher than those in other regions [17, 21]. A systematic investigation of the Kanzaki River system by our group revealed that there is a single source of PFOA within the Ai River [17], which was confirmed by Nguyen et al. [21]. The concentrations of PFOA in other countries are also shown in Table 1 [24–27]. These values are relatively higher than the values in Japan, excluding the Kansai region. Local intense contaminations were also observed in other countries, for example, the Tennessee River near Decatur, the Ruhr River, and Etobicoke Creek. The identified sources could be related to fluorochemical manufacturers, sewage treatment plant effluents, and fire-fighting foam [17, 24, 25].

The current surface water PFOS contaminations are shown in Table 1. The PFOS concentrations in Japan were relatively high in the Kanto and Kansai regions [17, 22]. Sewage treatment plant effluents exhibited high concentrations of PFOS as well as PFOA. High concentrations of PFOS were found in wastewater around airports [17]. However, detailed information regarding the types of fire-fighting foams used was not available.

The concentrations of PFOS and PFOA in drinking water in Japan have been reported [28, 29]. The levels of PFOA were extremely high in the Kansai region, especially Osaka [28], where the water supply is mainly derived from the Yodo River. On the other hand, the PFOS levels in tap water were higher in the Kanto region than in other regions [29]. It is therefore possible that the serum levels of these compounds in residents may be proportional to the levels in tap waters.

Distributions of PFOA and PFOS in outdoor air and indoor dust in Japan

There are limited numbers of reports regarding airborne and indoor levels of PFOA and PFOS. Harada et al. [30] showed that the concentrations of PFOA detected within urban atmospheric particles were 50-fold higher than those of PFOS. The amounts of PFOA and PFOS in the respirable fraction (1.1–11.4 μm) ranged from 58.3 to 89.8% of the total amounts [31]. The levels of PFOS and PFOA were significantly higher in the urban atmosphere of Oyamazaki than in the suburban atmospheres of Morioka and Fukuchiyama [30, 32]. Across Japan, there was a tendency for PFOA to be the predominant contaminant of outdoor air, particularly in Osaka [33]. Boulanger et al. [34] reported that the mean concentration of PFOS in particulate-phase air samples was 6.4 pg/m^3 (SD 3.3) in the Great Lakes. In Manchester, PFOA and PFOS were both detected at relatively high concentrations (341 and 46 pg/m^3, respectively) [35].

The concentrations in indoor dust in Japan ranged from 18 to 3,700 ng/g dust for PFOA and from 7 to 2,500 ng/g dust for PFOS [36, 37]. Compared with outdoor dust, the PFOS levels in indoor dust were comparable, but there are few reports regarding the PFOA levels in indoor dust (Table 2). A study in the USA reported that indoor dust contained higher levels of PFOS than PFOA [38]. The variations in the proportions of various fluorochemicals may reflect the source signatures caused by the use of different composites during the application or manufacturing process [39] (Table 3).

The sources of PFOA in the environment remain unclear. However, degradation of fluorotelomer alcohols (FTOHs) with atmospheric lifetimes of approximately

Table 1 Levels of PFOA and PFOS in water in Japan and several other countries

Area	*n*	PFOA (ng/l)		PFOS (ng/l)		Ref.
		GM (GSD)	Range	GM (GSD)	Range	
River						
Hokkaido	1		0.4		1.9	[17]
Tohoku	15	1.1 (2.7)	0.1–4.2	1.2 (2.5)	0.3–4.6	[17]
Kanto	14	2.8 (3.6)	0.3–15.1	3.7 (3.9)	0.3–31.4	[17]
Kanto (Tsurumi River)	10		11.2–19.8		17.1–612	[22]
Chubu	17	2.5 (2.2)	0.3–16.3	1.1 (2.4)	0.3–6.0	[17]
Kansai	8	21.2 (6.2)	2.1–456.4	5.7 (3.6)	0.8–37.3	[17]
Kansai (Kanzaki River)	52		4.5–67,000		1.5–526	[17]
Kansai (Yodo River)	33	60.5 (4.0)	6–2568	7.1 (4.2)	0.8–123	[21]
Chugoku	9	1.5 (2.3)	0.5–8.1	1.0 (3.4)	0.4–25.1	[17]
Shikoku	7	3.0 (2.1)	1.4–13.8	1.1 (4.7)	0.2–14.9	[17]
Kyushu	8	1.3 (2.4)	0.2–3.3	0.7 (1.9)	0.3–1.7	[17]
Coastal water						
Hokkaido	1		1.9		2.1	[17]
Hokkaido	1				<2.5	[20]
Tohoku	2	2.0 (1.1)	2.1–2.1	1.0 (1.9)	0.6–0.9	[17]
Kanto (Funabashi)	1		32.2		2.6	[17]
Kanto	4			26	8–59	[20]
Kanto	3	166 (1.1)	154–192	20.1 (1.5)	12.7–25.4	[23]
Chubu (Toyohashi)	1		11.5		0.7	[17]
Kansai (Koshien Hama)	1		448		27.69	[17]
Kansai	3			8.7	<4–21	[20]
Chugoku	4				<4	[17]
Kyushu	5			4.8	<9–11	[20]
Okinawa	4				<2.5	[20]
Tap water						
Tohoku	15	0.3 (2.3)	0.01–1.0	0.2 (1.7)	0.1–0.5	[17]
Kanto (Tokyo)	19	<5	<5–25	6.4	<5–37	[29]
Kansai	15	15.3 (2.3)	4.9–42.2	3.8 (3.6)	0.3–12.7	[17]
Kansai (Osaka)	14	31	7.9–110	3.8	0.3–20	[28]
River						
Tennessee, USA	40	366 (1.5)	140–498	55.1 (2.0)	16.8–144	[24]
Etobicoke Creek, Canada	13		11–1.1 × 10^4		ND-2.2 × 10^6	[25]
Cape Fear Drainage Basin, USA	80	16.2	<0.05–287	20.0	<0.05–132	[26]
Rhine River, Germany	38	4.9 (2.9)	2–48	6.5 (1.9)	2–26	[27]
Ruhr River, Germany	22	102 (5.0)	9–3640	11.7 (2.7)	4–193	[27]

GM geometric mean, *GSD* geometric standard deviation, *ND* not detected

10–20 days is speculated to be a source of PFOA [40]. FTOHs are currently produced and used as intermediates for the synthesis of coatings, polymers, inks, adhesives, waxes, and so on. Oono et al. [41, 42] reported that the airborne levels of several FTOHs were significantly higher in the Kyoto-Osaka area than in other areas. Taken together, the higher levels of airborne PFOA in the Kyoto-Osaka area may be caused by the high levels of FTOHs in the air.

Levels of PFOA and PFOS in food and dietary intakes

PFOA and PFOS concentrations in food samples have been reported for food duplicates [33, 43] and total diet studies (TDSs) [44]. The estimated daily dietary intakes of PFOA and PFOS were within the same ranges in Japan and other countries. Although no geographical differences in the dietary intakes were obvious, the serum levels of PFOA were higher in the Osaka area [33, 45]. A TDS in Canada showed

Table 2 PFOA and PFOS levels in outdoor air and indoor dust in Japan and several other countries

Sampling site		*n*	Units	PFOA			PFOS			Ref.
				GM	GSD	Range	GM	GSD	Range	
Japan	Oyamazaki Town (on a highway) 2001/April 2002/March	12	pg/m^3 air				5.3	1.2	2.3–21.8	[32]
			ng/g dust				97.4	1.2	38.0–427.4	
		12	pg/m^3 air	263	2.4	71.8–919.4	5.2	1.4	2.5–9.8	[30]
			ng/g dust	3,413	2.4	469–9049	72.2	1.8	19.7–168.0	
	Fukuchiyama City (on a local road) 2001/April 2002/March	12	pg/m^3 air				0.6	1.3	ND-2.1	[32]
			ng/g dust				19.2	1.2	ND-60.6	
	Morioka City (on a local road) 2003/July	8	pg/m^3 air	2.0	1.2	1.6–2.6	0.7	1.4	0.5–1.2	[30]
	Japan (20 sites) 2004	20	pg/m^3 air	9.0		6.0–2500	1.8		<0.1–30	[33]
	Indoor dust (general home)	16	ng/g dust	178	2.6	69.0–3700	39.5	3.9	11.0–2500	[37]
	Indoor dust (0.075–1 mm) (general home)	20	ng/g dust	36.1	1.5	18–89	19.9	1.6	7–41	[36]
Other	Lake Ontario (over a lake)	8	pg/m^3 air				6.4	3.3		[34]
	Manchester, UK 2003/July	2	pg/m^3 air	Mean 341			Mean 46			[35]
	Indoor dust, Ohio and North Carolina (general home)	102	ng/g dust	Median 142		<10–1960	Median 201		<8.9–12,100	[38]

GM geometric mean, *GSD* geometric standard deviation, *ND* not detected

Table 3 PFOA and PFOS levels in food samples and their daily intakes

Sampling site	*n*	Units	PFOA			PFOS			Ref.
			GM	GSD	Range	GM	GSD	Range	
Ten sites in Japan	50	ng/g wet weight	<0.01		<0.01–0.024	0.012	2.6	<0.0017–0.12	[33]
Osaka	10	ng/day	61.4	1.7	22.7–124	76.3	1.6	32.1–180	[45]
		ng/g wet weight	0.022	1.7	0.008–0.040	0.027	1.5	0.015–0.057	
Miyagi	10	ng/day	44.4	1.5	29.0–90.4	61.5	2.5	18.5–267	[45]
		ng/g wet weight	0.019	1.3	0.012–0.031	0.026	2.3	0.008–0.087	
			Median	Average	Range	Median	Average	Range	
Canada		ng/day		70			110		[44]
Germany	31	ng/day	169		91.9–839	90.4		47.7–371	[43]

GM geometric mean, *GSD* geometric standard deviation

that dietary intake of PFOS was mainly derived from beef and fish, while PFOA originated from beef and microwave popcorn [44]. Owing to PFOS bioaccumulation in the environment, fish seem to represent important routes of exposure [46]. In addition, several food packaging coatings for oil- and moisture-resistance are made from fluorochemicals that may degrade into PFOA and PFOS [47].

Estimated daily intakes of PFOA and PFOS in Japanese

Exposure levels to PFOA and PFOS have been estimated using their concentrations in indoor dust, outdoor air, tap water, consumed items, and diet. It was estimated that the adult intake of indoor dust is 50 mg/day [48], the adult intake of tap water is 1.3 l/day, and adult humans inspire 13.3 m^3 of air/day; 69 and 74% of particles in air are respirable for PFOA and PFOS, respectively, and PFOA and PFOS in each medium are completely absorbed into the body.

The estimated exposure through food was predominant for both PFOA and PFOS (Table 4). Among the estimates, exposure via food consumption was the major source, followed by tap water and indoor dust. Exposure via tap water was more intense in the Kansai region than in the Tohoku region. Information regarding exposure levels via

Table 4 Estimates of adult exposures (ng/day) to PFOA and PFOS

Source	Kansai		Tohoku		Notes	Ref.
	PFOA	PFOS	PFOA	PFOS		
Water	19.9	4.9	0.4	0.3	Calculated from tap water concentrations (GM) for Kansai and Tohoku	[17]
Indoor dust	8.9	2.0	8.9	2.0	Calculated from vacuum cleaner dust concentrations (median) for Osaka	[37]
Ambient air	2.4	0.1	0.02	0.01	Calculated from airborne dust concentrations (GM) for Kyoto and Iwate	[30]
Food	61.4	76.3	44.4	61.5	Estimated from food duplicate concentrations (GM) for Osaka and Miyagi	[45]
Total	92.6	83.3	53.7	63.8		

GM geometric mean

indoor dust and food is still insufficient. Moreover, exposure levels to precursors of PFOA and PFOS have not been evaluated. Even if these estimates for PFOA and PFOS exposure are uncertain, they play important roles in allowing speculation for sources of exposure that may lead to regional differences in serum levels.

Compared with intakes of these compounds, analyses of 24-h pooled urine from residents in Kyoto revealed levels of 17.6 and 13.3 ng/day for PFOA and PFOS, respectively [49]. Although fecal excretion of these chemicals remains unclear, such limited excretion in urine was in clear contrast to the case for rodents and monkeys [49], suggesting unique pharmacokinetic behaviors in humans.

Serum levels of PFOA and PFOS in Japanese

Figure 1 shows the serum concentrations of PFOA and PFOS in Japanese [50]. There were significant geographical differences in PFOA and PFOS serum concentrations for both males and females. Residents belonging to the Kansai region (Kyoto, Osaka, and Hyogo) exhibited significantly higher serum PFOA levels. Serum PFOS levels in the Kansai region were significantly higher than those in the Tohoku and Chubu regions (Akita, Miyagi, Gifu, and Fukui) and comparable to those in Yamaguchi, Kochi, and Okinawa. The serum PFOS and PFOA levels in other countries are shown in Fig. 1. The serum PFOS levels were higher in the USA than in Japan and Europe, while the serum PFOA levels were comparable among the USA, Europe, and Japan, except for the Kansai region [19, 51, 52].

Several factors influencing the serum levels of these compounds have been reported. Sex-related differences in the serum concentrations of PFOS and PFOA were observed and the concentrations of PFOS and PFOA were higher in males than in females [49, 51, 52]. There were positive correlations between age and PFOS and PFOA levels only in females [49]. Multiparous women had lower PFOS and PFOA levels than nulliparous women [10]. With regard to ethnicities, Mexican Americans had lower levels than non-Hispanic blacks and whites in the USA. Higher education was associated with higher PFOS and PFOA levels [53].

Time trends of the serum levels of these compounds have been presented by several researchers (Fig. 2). Harada et al. [18] revealed that the serum concentrations increased 3-fold for PFOS and 14-fold for PFOA between 1977 and 2003 in Yokote in Miyagi prefecture. The PFOA concentrations in Kyoto increased by 4.4-fold from 1983 to 1999 [50]. In the USA, the PFOS and PFOA concentrations increased between 1974 and 1989, and reached plateau levels in 1989 [54]. In China, the serum levels of both PFOA and PFOS have increased significantly over recent years and reached the corresponding levels in Japan [55]. After 3M Company phased out PFOA and PFOS production, decreases in the PFOA and PFOS concentrations were observed in the USA [56]. It should be confirmed whether similar decreases also have been observed in other countries.

Toxicokinetics of PFOA and PFOS

A recent study revealed interspecies differences in the pharmacokinetics of PFOA and PFOS. The mean serum half-lives of PFOA and PFOS in humans were 3.5 and 5.4 years, respectively [57]. These long half-lives explain why PFOA and PFOS tend to accumulate in humans. In contrast, the half-lives in experimental animals were orders of magnitudes shorter than those in humans. The serum half-lives of PFOA in Wistar rats were reported to be 5.68 days for males and 0.08 days for females [58], whereas those in primates were 5.6 days for males and

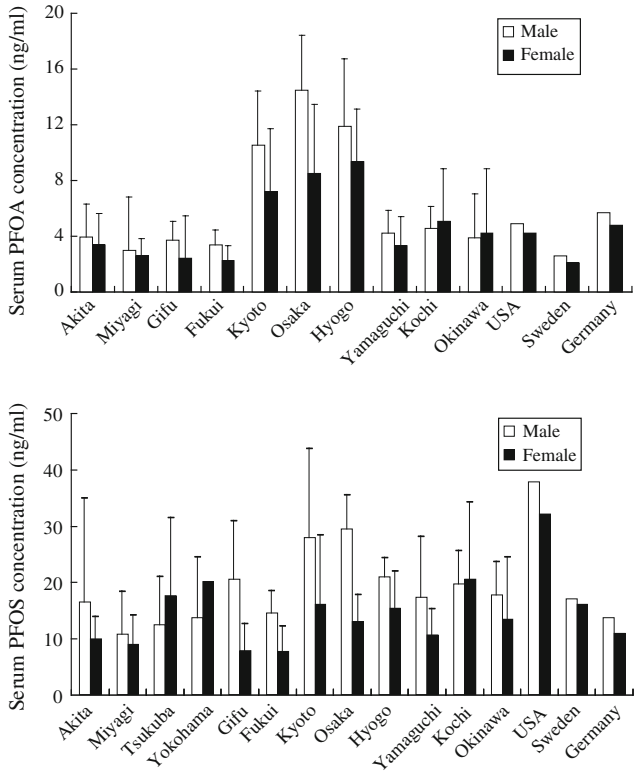

Fig. 1 Human serum concentrations of PFOA and PFOS in Japan and several other countries collected from 2000 to 2005. The data for Tsukuba, Yokohama, and other sites in Japan are taken from Taniyasu et al. [20] and Harada et al. [18, 50]. The data are geometric means and geometric standard errors in Japan. For the USA and Sweden, the data are geometric means reported by Olsen et al. [19] and Kärrman et al. [52], respectively. For Germany, the data are medians reported by Fromme et al. [51]

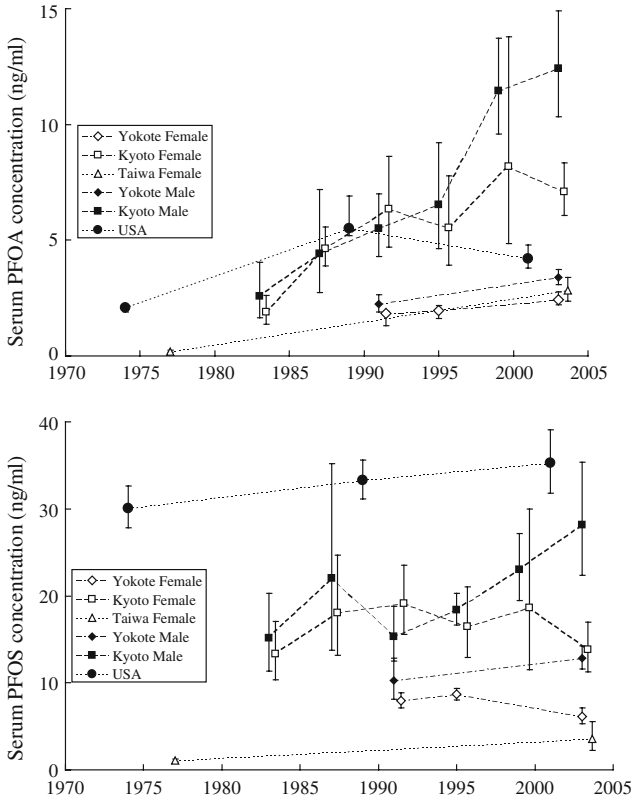

Fig. 2 Time trends in PFOA and PFOS serum levels in Japan [18, 50] and the USA [54]. Data are geometric means and geometric standard errors

2.7 days for females in Japanese macaques, and approximately 1 month for both sexes in cynomolgus monkeys [59, 60]. The serum half-lives of PFOS were longer than those of PFOA, comprising more than 89 days in male CR:CD rats [61], and approximately 100 days in both male and female cynomolgus monkeys [62].

In Cr:CD rats, intravenously administered PFOA and PFOS were excreted via the urine (67 and 18%, respectively) and feces (4.4 and 8.0%, respectively) [63, 64]. However, the serum clearances of PFOA via urine in humans were 300–1,000-fold lower than those in Wistar rats and Japanese macaques (Table 5) [49]. A critical role of the resorption process was supposed as a determinant for the large species differences in renal excretion of PFOA [65]. Several organic anion transporters (OATs) have been investigated. Nakagawa et al. [66] found that OAT1 (Slc22a6) and OAT3 (Slc22a8) mediated transport of PFOA in both humans and rats, while OAT2 (Slc22a7) did not. Rat Oatp1 (Slc21a1) had transport activity for PFOA, which may be involved in the resorption process and cause sex-related differences in rats, although no human ortholog for rat Oatp1 exists [67]. There have been few studies regarding the species difference in urinary excretion of these compounds, and further studies are warranted in this area.

Biliary excretion of PFOA and PFOS has emerged as a major elimination route in humans owing to the poor urinary excretion. PFOA and PFOS were detected in human bile samples at similarly high levels to those detected in serum samples [68]. The ratio of PFOS concentrations (bile/serum: 0.60) was significantly higher than that for PFOA concentrations (bile/serum: 0.21). The biliary excretion rates of PFOA and PFOS in humans were estimated to be 1.06 and 2.98 ml/(kg day), respectively (Table 5). Although elimination of PFOA and PFOS in feces remains unexplored, available evidence in rats suggests that trace amounts were excreted via this route owing to enterohepatic circulation of these chemicals [63]. Such enterohepatic circulation of PFOS and PFOA may account for their long half-lives in humans.

PFOS and PFOA have been detected in cerebrospinal fluid (CSF) in humans [68]. The PFOA and PFOS levels in CSF were approximately 1% of the corresponding levels in serum, suggesting that PFOA and PFOS cannot freely pass through the blood–brain barrier. The reported brain-to-

Table 5 Estimated clearances of PFOA and PFOS in rats, monkeys, and humans

			Serum half-life (days)	Total clearance [ml/(day kg)]	Urinary excretion [ml/(day kg)]	Biliary excretion [ml/(day kg)]	Menstrual bleeding [ml/(day kg)]
PFOA	Wistar rats[a]	Male	5.63	50.4	46.1	3.30	NA
		Female	0.08	2233	1054	3.52	NA
	Cynomolgus monkeys[b]	Male	20.9	6.0	NA	NA	NA
		Female	32.6	4.2	NA	NA	NA
	Japanese macaques[c]	Male	5.6	37.1	15	NA	NA
		Female	2.7	77.0	32	NA	NA
	Humans[d]		1387	0.070	0.030	1.06	0.028[g]
PFOS	CR:CD rats[e]	Male	>89	NA	NA	NA	NA
	Cynomolgus monkeys[f]	Male	132	NA	NA	NA	NA
		Female	110	NA	NA	NA	NA
	Humans[d]		1971	0.077	0.015	2.98	0.028[g]

NA not available

[a] Half-lives, total clearance, and urinary excretion were reported by Kudo et al. [58]. Biliary excretion was estimated from a report by Vanden Heuvel et al. [64]

[b] Half-lives in an intravenous study were reported by Butenhoff et al. [60]. Total clearances were calculated based on volume distributions of 181 and 198 ml/kg for males and females, respectively

[c] Half-lives and renal clearance were reported by Kudo and Kawashima [59]. Total clearances were calculated based on a volume distribution of 300 ml/kg

[d] Half-lives in retired workers were reported by Olsen et al. [57]. Urinary and biliary excretions were reported by Harada et al. [49, 68]. Total clearance was calculated based on volume distributions of 220 ml/kg for PFOS and 140 ml/kg for PFOA [65]

[e] Cited from an intravenous study by Gibson and Johnson [61]

[f] Cited from a report by Noker and Gorman [62]

[g] Menstrual serum loss was assumed to be 42 ml/month

blood ratios of 0.17 for PFOA and 0.26 for PFOS in cadavers were consistent with low partition to CSF [69]. However, the occurrence of these chemicals in CSF raises concerns that the central nervous system may be one of the target organs of PFOA and PFOS toxicities.

Sex-related differences in elimination

The sex-related differences in the renal clearances of PFOA in rats suggest that hormone-regulated elimination is probably involved to a certain extent in this species [58]. The expressions of OATs are known to be regulated by sex steroids and/or growth hormones in rodents, but not in humans [70].

Sex-related differences in the serum levels of these compounds were reported in humans, but there was no difference in renal clearance between males and females [49]. The observed difference may be explained by female-specific excretion routes, such as menstrual blood loss, lactation, and direct maternal-fetal transfer. Menopausal females had significantly higher serum concentrations than menstrual females in a 20–50-year age group [49]. With regard to excretion through lactation, PFOS and PFOA were detected in breast milk samples [71]. The mean ratios between the milk and serum concentrations were 0.01:1 for PFOS and 0.02:1 for PFOA, resulting in clearances of 6–12 ml/day. Decreases in the concentrations of PFOS and PFOA were reported between the first and second trimesters [8]. Several researchers have reported the concentrations of PFOA and PFOS in maternal and fetal cord serum samples [72]. In addition, PFOS and PFOA concentrations decreased with increased parity of mothers [10], implying that maternal-fetal transfer may reduce the maternal stores. Moreover, it is possible that hormonal changes in body composition or alterations of protein-binding affinity may affect the distribution and elimination of PFOS and PFOA [73, 74].

Toxicology of PFOA and PFOS

Epidemiological studies

There have been a number of reports on the health effects of PFOA and PFOS (Table 6). One epidemiological study conducted by 3M Company suggested an increase in prostate cancer mortality among workers exposed to PFOA [11]. Another study conducted by 3M Company revealed an increased mortality from bladder cancer among workers

Table 6 Epidemiology and in vivo toxicities of PFOA and PFOS

Species	Humans	Monkeys	Rodents
PFOA			
Carcinogenicity	Prostate cancer mortality [11]		Liver tumors, pancreatic acinar cell tumors, Leydig cell tumors [79]
Hepatotoxicities	Slight increases in total cholesterol, low-density lipoprotein, very low-density lipoprotein, gamma glutamyl aminotransferase, and aspartate aminotransferase [77]	Hepatomegaly accompanied by mitochondrial proliferation, no peroxisome proliferation [85]	Peroxisome proliferation, increased hepatocyte hypertrophy, increased labeling index [83]
Developmental toxicities	Decreased birth weight [8, 10]		Early pregnancy loss, increased neonatal mortality, delayed eye opening, growth deficits, altered pubertal maturation [87, 91]
Behavioral and neurotoxicities		Decreases in food consumption and body weight [85]	Decreased food intake, reduced habituation and hyperactivity, hypoactive response to nicotine [94, 96]
Other	Higher prevalence of angina, myocardial infarction, stroke, chronic bronchitis, shortness of breath on stairs, asthma [78]		
PFOS			
Carcinogenicity	Bladder cancer mortality [9]		Hepatocellular adenoma, thyroid follicular cell adenoma [80]
Hepatotoxicities	Possible increase in cholesterol, decrease in high-density cholesterol, initial decrease and subsequent increase in total bilirubin [76]	Decreased body weights, increased liver weights, lowered serum total cholesterol levels, lowered estradiol levels, no peroxisome proliferation [86]	Peroxisome proliferation, mild increase in hepatic palmitoyl CoA oxidase [80]
Developmental toxicities	Decreased birth weight, ponderal index, and head circumference [10]		Increased relative liver weight of pups, delayed eye opening, neonatal death due to intracranial blood vessel dilatation and lung atelectasis, decreased natural killer cell function in male pups [88–90]
Behavioral and neurotoxicities		Decreases in food consumption [86]	Decreased food intake [95], reduced habituation and hyperactivity, hypoactive response to nicotine [96]

exposed to PFOS [9]. Hepatic, lipid, and thyroid parameters, which are known toxicological effects in rodents, showed inconsistent associations with serum levels of PFOS and PFOA in fluorochemical workers [75–77]. Besides hepatotoxicity, higher prevalences of cardiovascular and respiratory diseases were reported in plaintiffs or potential plaintiffs in a lawsuit, which might be biased [78]. Two epidemiological studies in the USA and Denmark showed an inverse correlation between PFC concentrations (cord or maternal blood) and birth weight [8, 10]. In the populations examined in these studies, the PFC levels were much lower than those in animal experiments, which may suggest species differences in susceptibility to PFCs.

Hepatotoxicity and molecular targets of PFOA and PFOS

Although these chemicals were found to be carcinogens for rodents [79, 80], they were not genotoxic in umu tests [81]. It should be further investigated whether the hepatocarcinogenic potencies are in proportion to the degrees of induction of peroxisome proliferator-activated receptor-alpha (PPARα), to which these chemicals bind as ligands [82]. In PPARα-null mice, hepatomegaly induced by PFOA was still observed, suggesting that another mode of action exists [83], such as constitutive activated/androstane receptor actions [84].

The expression and activation of PPARα differ between humans and rodents. In monkeys, PFOA and PFOS caused hepatomegaly, but did not lead to peroxisome proliferation [85, 86]. Therefore, results generated in rodents cannot be simply extrapolated to humans. In addition, a number of studies have revealed that the toxicological target organs of PFOS and PFOA may differ between humans and rodents, such as developmental toxicities in humans and carcinogenicity and liver toxicity in rodents.

Developmental toxicity

The reproductive and developmental toxicities of these chemicals toward humans are of particular concern [87]. Prenatal as well as postnatal toxicities of PFOA and PFOS were observed in rats and mice, including increased liver weights, growth lags, delayed development, and suppressed immune functions [88–90]. PFOA had significant effects on fetal growth and development in males, but much lesser effects in females. The difference in sensitivity was presumed to be due to the sex-related difference in PFOA elimination. Some developmental toxicities of PFOA, such as delayed eye opening and deficits in postnatal weight gain, were diminished in PPARα-null mice [91], whereas PFOS-induced neonatal lethality and delayed eye opening are not dependent on PPARα [92].

Neurotoxicity

PFOS may have effects on the neuroendocrine system in rats and mice. Increased corticosterone concentrations in serum and norepinephrine in the hypothalamus were induced by PFOS in mice, indicating that PFOS stimulates the stress axis [93]. Observed decreases in food intake caused by PFOA and PFOS were mediated via the activation of hypothalamic urocortin 1 and 2, respectively [94, 95]. PFOS exposure also induced behavioral effects in mice, such as anxiety and spatial memory loss [96]. These observations suggested neurotoxic effects of PFOA and PFOS, although the target molecules in the central nervous system remain unclear.

PFOS and PFOA were reported to exhibit electrophysiological effects on action potentials and currents in isolated guinea-pig ventricular myocytes, cerebellar Purkinje cells, and protozoa [97–99]. In addition to excitable cells, PFOS activated voltage-dependent Ca^{2+} channels (VDCCs) and increased intracellular Ca^{2+} concentrations in non-excitable tracheal cells [100]. PFOS also inhibited neurite growth and suppressed synaptogenesis in cultured hippocampal neurons through VDCCs [101]. The mechanisms of these effects are hypothesized to involve incorporation of PFOS and PFOA into the outer cell membrane, which would decrease the steepness of the transmembrane potential gradient and result in hyperpolarizing shifts of both the activation and inactivation of voltage-gated ionic channels.

Conclusions

Perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and related compounds have been used for many applications. The chemical stability of perfluorinated alkyl chains results in their persistence in the environment and organisms.

These compounds have been detected in various areas of Japan. In the Kansai region, environmental contamination by PFOA and related compounds was more intense than in other regions. Serum PFOA levels have been increasing insidiously throughout the last 20 years in Kyoto residents, and also in northern Japan. The geographic heterogeneity in the exposure intensities of PFOS and PFOA is likely, at least in part, to be associated with industrial activities. Although the estimated daily intakes of PFOS and PFOA remain somewhat uncertain, intake from drinking water is considered to represent a major component and could explain the regional differences in Japan. If this is indeed the case, identification of the sources and appropriate control of the release of PFCs urgently require discussion.

There are large interspecies differences in the toxicokinetics of these compounds. In particular, their poor renal clearances and long half-lives in humans suggest uncertainty regarding exposure assessment and extrapolation of test dosages. These qualitative differences may involve transporters in various organs.

The toxicological susceptibilities of humans to PFCs may also be higher than those of rodents. Epidemiological studies on birth weight in the general population revealed inverse correlations with PFOA and PFOS levels, which were 100–1,000-fold less than those in animal experiments. Although human PPARα has relatively low activity in comparison to rodent PPARα, other molecular targets of PFOS and PFOA may exist.

PFOA and PFOS are now under control and regulation in various countries. Monitoring of these compounds should be continued to evaluate measurements of PFCs. In closing, there are growing concerns regarding the developmental toxicities of these compounds toward human fetuses, particularly in the Kansai region. Further studies regarding the issue of whether adverse developmental effects occur are urgently required.

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