Renal clearances of perfluorooctane sulfonate and perfluorooctanoate in human, and their species-specific excretion

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Abstract

Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are detected in the environment, as well as more specifically in wildlife and human. However, the toxicokinetic aspects of perfluorochemicals in human are unclear. In this study, we measured concentrations of PFOA and PFOS in subjects who had lived in Kyoto city for more than 10 yr. The serum concentrations of PFOA and PFOS were higher in females without menstruation than those with menstruation ($p<0.01$), but in males did not change by age; the levels in females reached those in males at an age of ≥60 yr. We then determined the renal clearances of PFOA and PFOS in young (20-40 yr old, N=5 for each sex) and old (≥60 yr old, N=5 for each sex) subjects of both sexes. All young females were menstruating, while all old females were not. The renal clearances were 10^{-5}-fold smaller than the glomerular filtration rate in human, suggesting the absence of active excretion in human kidneys. The renal clearances of PFOA and PFOS were approximately one-fifth of the total clearances based on their serum half-lives, assuming a one-compartment model. The sex differences in renal clearance that have been reported in rats and Japanese macaques were not found in our human subjects. We tried to build a one-compartment pharmacokinetic model using the reported half-lives in human. The model was simple but could predict the serum concentrations in both males and females fairly well. We therefore suggest that an internal dose approach using a pharmacokinetic model should be taken because of the large species differences in kinetics that exist for PFOA and PFOS.

Key words: Perfluorooctane sulfonate, perfluorooctanoate, serum, urine, renal clearance

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Ethical issues

Blood and urine samples were taken after formal informed consent was obtained from each participant. The research protocol was reviewed and approved by the ethical committee of Kyoto University.

1. Introduction

Perfluorochemicals (PFCs), of which perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are representative, are a class of specialty chemicals used in a variety of applications, for example, in lubricants, paints, cosmetics and fire-fighting foams (U.S. EPA, 2000; Kissa, 2001). Even though PFOS was seen as an important perfluorinated surfactant, the manufacturer 3M recently (in 2002) phased it out after 50 yr of production (Renner, 2001). The release, production and use of these chemicals are regulated now by various governmental bodies.

PFOS has been detected globally in a variety of living organisms, including human (Olsen et al., 2003; Harada et al., 2004b) and wildlife (Giesy and Kannan, 2001). This worldwide distribution of PFOS has been attributed to its resistance to degradation in ecological systems (U.S. EPA, 2000) and its bioconcentration (Martin et al., 2003). In contrast, PFOA has only been detected in selected areas (Kannan et al., 2002; Martin et al., 2004).

Species and sex differences have been reported in the toxicokinetics of PFOA and PFOS. The serum elimination half-life for PFOA in Wistar rats was 5.68 d for males and 0.08 d for females (Kudo et al., 2002), while in primates the values were 5.6 d for males and 2.7 d for females in Japanese macaques and approximately 1 mo for both sexes in cynomolgus monkeys (Kudo and Kawashima, 2001; Butenhoff et al., 2002). The average apparent serum elimination half-lives for PFOS were 7.5 d in male Cr:CD rats and approximately 200 d in male and female cynomolgus monkeys (OECD, 2002; Seacat et al., 2002). An epidemiological study of retired employees involved in the production of PFCs revealed that the human serum elimination half-lives were 4.37 yr for PFOA and 8.67 yr for PFOS (Burris et al., 2002). In addition, our recent report clearly demonstrated that the serum concentrations of PFOA and PFOS in human were higher in males than in females (Harada et al., 2004b). These data suggest a large difference in

the elimination kinetics among species and sexes.

Kudo et al. (2002) demonstrated that the organic anion transporters (OATs) *rOAT2* and *rOAT3* might be involved in the renal excretion of these chemicals in Wistar rats (Kudo et al., 2002). Furthermore, the expressions of these transporters are known to be regulated by sex steroids and/or growth hormones (Buist et al., 2003). Therefore, a reasonable hypothesis would be that a hormone-dependent active transport system is involved in the renal clearances of PFOA and PFOS in human. In the present study, we aimed to evaluate the effects of age on the serum concentrations of these chemicals in both males and females. We also aimed to evaluate the renal clearances of these chemicals in human. Finally, we developed a pharmacokinetic model to predict serum concentrations of PFOA and PFOS in human of both sexes at various ages. The present data provides an insight into the elimination of these chemicals in human.

2. Materials and Methods

2.1. Experimental design

We conducted two studies. In Study 1, we evaluated the serum concentrations of PFOS and PFOA in both females and males of various ages who have been residents of Kyoto city for more than 10 yr (designated as Kyoto city dwellers). Kyoto, in the Kinki region of Japan, is an urban area with a population of approximately 1,464,300. The rationale for limiting study participants to Kyoto city was that serum concentration levels are reportedly higher in Kyoto city dwellers than in residents of areas outside the Kinki region (Harada et al., 2004b). In addition, nearly all Kyoto city dwellers use the same source of drinking water and are supposed to be exposed to the similar levels and qualities of air-borne dust, which are two suspected major routes of exposure (Harada et al., 2003, 2004a; Saito et al., 2004; Sasaki et al., 2003). Therefore, we considered exposure intensities among Kyoto city dwellers to be homogeneous (Harada et al., 2003,

2004a; Saito et al., 2004; Sasaki et al., 2003), thus making it possible to isolate the effects of age and sex from geographical factors. In Study 2, we determined the renal clearances of PFOS and PFOA in young (20-40 yr old) and old (≥60 yr old) subjects of both sexes, since the renal clearances should be larger in young females than old females or males if a sex hormone-dependent active transport system is involved. Finally, we compared the renal clearances observed in human with those in other species.

2.2. Study participants

Samples were collected from participants between January and March 2004. Employees of fluorochemical manufacturing factories and regular blood donors were not included among the participants. For Study 1, participants, Kyoto city dwellers ≥10 yr, were recruited through universities and local communities. Participants donated 4 mL of blood, and were interviewed with regards to their age and residential history. We also asked female participants whether or not they were regularly menstruating, and if not, when menstruation ceased.

For Study 2, young participants were recruited from students; residential area was not a selection criterion for these participants, and elderly participants, Kyoto city dwellers ≥10 yr, were recruited from local social clubs. Participants collected 24-hr pooled urine samples, and donated 10 mL of blood at the end of urine collection. When these samples were collected, the participants were interviewed with regards to their age, height, weight, current medication, and medical and residential histories. Those who had a medical history of renal diseases were not included. Female participants were asked about menstrual cycles as in Study 1.

Serum was separated from red blood cells (RBC) and other cellular components on the day of collection by centrifugation at 3000 rpm for 15 min. Serum and urine were

stored at –20°C until use. Blood and urine samples were taken after formal informed consent was obtained from each participant. The research protocol was reviewed and approved by the ethical committee of Kyoto University.

2.3. Reagents

Heptadecafluorooctane sulfonic acid potassium salt (FW.538.22), used as a standard for PFOS, and pentadecafluorooctanoic acid ammonium salt (FW.431.10), used as a standard for PFOA, were purchased from Fluka (Milwaukee, WI). The purities of these standards were greater than 98%; we did not correct the reported concentrations according to purity. 1H,1H,2H,2H-tetrahydro-perfluorooctane sulfonate was synthesized as an internal standard (Wako Pure Chemicals, Osaka Japan), and its purity was greater than 99%.

2.4. Determination of PFOS and PFOA in serum and urine

Prior to extraction, the internal standard was added to each sample. For serum samples, we employed the extraction process developed by Hansen et al. (Hansen et al., 2001) as previously reported (Harada et al., 2004b). For urine samples, we employed a previously reported extraction method for surface water samples (Saito et al., 2003). In a preliminary study, randomly selected urine samples (N=5) were subjected to acid hydrolysis (pH<0.1, concentrated HCl at 100°C without evaporation for 45 min). This procedure did not alter the yields of PFOA and PFOS, and we therefore eliminated this procedure for the other samples.

Each extracted solution was analyzed by liquid chromatography-mass spectrometry (LC/MS) as previously reported (Saito et al., 2003, 2004; Sasaki et al., 2003). The limit of detection (LOD) and limit of quantification (LOQ), defined as the lowest concentration at which the analytical process can reliably differentiate from the

background level, were considered to be three- and ten-fold larger than the signal-to-noise (S/N) ratio, respectively.

2.5. Renal clearance, total clearance and elimination by menstrual bleeding

The creatine levels in serum and urine were assayed by the alkaline picric acid method (SRL Inc., Japan). Renal clearance (CL_R: L/24 hr) was calculated as follows:

CL_R = Total amount of creatinine in 24-hr urine sample (μg/24 hr)/serum concentration of creatinine (μg/L) ------- Eq(1)

We assumed a one-compartment pharmacokinetic model for the elimination of PFOS and PFOA from the body (Harada et al., 2003), and with this assumption, the total clearance from the body (CL_{tot}: L/d/kg) was calculated as follows:

$$CL_{tot} = 0.693*V/(T_{1/2}) \quad \text{------- Eq(2)}$$

where V is the volume distribution (L/kg) and $T_{1/2}$ is the biological half-life (d). It should be noted that in the one-compartment model, the serum elimination half-life is equal to the biological half-life.

2.6. One-compartment kinetic model simulation

We developed a one-compartment pharmacokinetic model to predict serum levels of PFOA and PFOS in the Study 1 population. In the one-compartment model, the serum concentration at T (days) was expressed as:

$$V\frac{dC(T)}{dT} = E - kC(T) \text{ ---- Eq(3)}$$

$$k = k_{tot} + k_m \text{ ---- Eq(4)}$$

$k_{tot} = CL_{tot}$ ---- Eq(5)

where V and C(T) (mg/L) represents the volume distribution (mL) and serum concentration (ng/mL) of PFOS and PFOA at time T days after initiation of exposure, respectively. Other parameters represent: E, Daily intake (ng/day); k, Clearance (mL/day); k_{tot}, Total clearance of males (mL/day); k_m, Menstrual blood loss (mL/day).

Since V cannot be measured directly, we estimated it by nonlinear parameter estimation using reported data from various species (Kudo and Kawashima, 2001; Kudo et al., 2002; Seacat et al., 2002) with the method reported by Koizumi (1989). We incorporated menstrual bleeding as one of the elimination routes. Menstrual bleeding was assumed to occur monthly with a blood loss volume of 70 mL (Hallberg et al., 1966), and the hematocrit value of females was taken as 40% (Henry, 2001). We also assumed that PFOA and PFOS were fractioned in serum, but not in RBC.

Since daily intake, E, cannot be measured directly, we estimated it by nonlinear parameter estimation as previously reported (Koizumi, 1989). The validity of the model was evaluated based on whether the predicted values could simulate the observed values in Study 1.

2.7. Statistics

For statistical analysis, participants were grouped into 4 categories (Young Males: 20-40 yr old; Young Females: 20-40 yr old; Old Males: ≥60 yr old; and Old Females: ≥60 yr old). Comparison of means was performed by multiple-way ANOVA or the Student's t-test when appropriate. $P<0.05$ was considered significant. All statistical analyses were carried out using SAS software (SAS Institute, 2000).

3. Results

3.1. Study population

The number and demographic features of the participants in Study 1 are summarized in Table 1. In total, 48 Kyoto city dwellers (20 males and 28 females) participated, and a residential history of longer than 10 yr was confirmed for all Kyoto city participants.

The number and demographic features of the participants in Study 2 are summarized in Table 2. In total, 20 subjects (10 males and 10 females) participated, of whom 14 (6 males and 8 females) were Kyoto city dwellers for ≥10 yr and 6 (4 males and 2 females) moved to Kyoto city from other districts within the past 6 mo to 3 yr. Six of the 20 subjects had medical histories: one hypertension, one hyperlipidemia and thyroidectomy, one breast cancer and three other diseases. Five subjects in the old male and female groups were taking antihypertensives, vitamins and antiflatulents, analgesics, musk, or antihyperlipidemic medications regularly. The female participants in the young group had regular menstrual cycles, while none of the female participants in the old group did; indeed at least three yr had elapsed since the last menstrual cycle. Creatine clearances of all participants were within the normal limits (range, 70.4 to 129.3 mL/min), and therefore all participants were included in this study.

3.2. Serum PFOS and PFOA concentrations

The serum levels of PFOA and PFOS are shown in the Fig. 1. For all serum samples, the PFOA and PFOS levels were greater than the LOQ (0.1 ng/mL). The figure suggested an age-associated increase in serum concentrations in females. We thus grouped the population into two age subgroups (≤50 yr vs. 50< yr) ad hoc. Females in the age group ≤50 yr had menstrual cycles while females in the age group 50< yr did not. Two-way ANOVA showed no significant interaction between age and sex (Table 3).

Comparisons with regards to age and sex were therefore conducted independently. The mean serum PFOS and PFOA concentrations were significantly higher in male than female Kyoto city dwellers in the 20-50 yr old age group (Table 3), which is consistent with a previous report (Harada et al., 2004b). In contrast, females over 51 yr old, all of whom were menopausal, had significantly higher serum concentrations than females in the 20-50 yr old age group who were actively menstrual. There were no differences in the serum levels of PFOA and PFOS between males and post-menopausal females.

3.3. PFOS and PFOA concentrations in urine and renal clearances

Acid hydrolysis of urine samples caused no substantial changes in the levels of PFOA and PFOS (data not shown), indicating that conjugates are not detectable metabolites of these chemicals, if present at all. Neither medication nor medical histories had significant effects on serum levels of PFOA and PFOS (data not shown). The urine levels and renal clearances of PFOA and PFOS are shown in Table 4. All urine samples were quantified over the LOQ (1 ng/mL). There were no significant differences in the renal clearances of PFOA or PFOS with regards to sex, age group, medication and medical or residential histories (data not shown). The mean renal clearance values (n = 20, mL/d/m^2 ± S.D. and mL/d/kg ± S.D.) for PFOA were 1.06 ± 0.47 and 0.030 ± 0.013 respectively, and for PFOS were 0.52 ± 0.31 and 0.015 ± 0.010, respectively.

3.4. Comparisons of PFOA and PFOS clearances among various species

The volume distribution, V, for PFOA was estimated to be 0.3 L/kg in rat (Kudo et al., 2002) and monkey data (Kudo and Kawashima, 2001) by nonlinear parameter estimations. The V for PFOS was estimated from monkey data (Seacat et al., 2002) to be 0.3 L/kg (Harada et al., 2003). Thus, we assumed the volume distributions for PFOA

and PFOS to be 0.3 L/kg for human. The total clearances of PFOA and PFOS in rat, monkey and human were estimated by Eq.(1) according to the reported $T_{1/2}$ (Table 5).

In rat, the renal clearance, CL_R, of PFOA was more than 20-fold larger in females than males. For female rats, CL_R was 8.6% of the glomerular filtration rate (GFR) and was significantly greater in females than males, indicating hormone-sensitive active excretion from the renal tubuli. Renal excretion was the major route of elimination in rats with regards to the total clearance, CL_{tot}. In Japanese macaques, CL_R was two-fold larger in females than males, but was less than 0.8% of the GFR, suggesting that active transport was unlikely in the renal tubuli. Renal excretion explained about 40% of the CL_{tot}. In contrast, only negligible amounts were excreted in the urine of both sexes in humans. CL_R was only about 1×10^{-3}% of the GFR, indicating the absence of active excretion in human kidneys. For PFOS, CL_R was also small. In both sexes, the values were less than 1×10^{-3}% of the GFR, again suggesting the absence of active excretion from the renal tubuli in humans.

3.5. Prediction of serum concentrations of PFOA and PFOS in human by one-compartment kinetic modeling

We assumed that the half-lives of PFOA and PFOS were 1573 and 3165 days for males (Burris et al. 2002) and varied $T_{1/2}$ by ± 25% in the simulation. Clearance in females was assumed to be the same as that in males except for menstrual blood loss. Body weight was assumed to be 60 kg for males and 50 kg for females, which is the Japanese standard. In females, menstruation was assumed to start at 10 yr and stop at 50 yr. We also assumed that serum concentrations were 13 ng/mL for PFOA and 30 ng/mL for PFOS in male and 8 ng/mL for PFOA and 13 ng/mL for PFOS in females of reproductive age (Table 3). Based on Eqs(3-5), daily intakes of PFOA and PFOS were estimated to be 1.7 ng/kg/day for PFOA and 1.8 ng/kg/day for PFOS, respectively. The

results of the simulation were superimposed on the serum concentrations of PFOA and PFOS for the Kyoto city dwellers (Fig. 1).

4. Discussion

The present study revealed novel findings in terms of the toxicokinetics of PFOA and PFOS. We clearly demonstrated that the serum concentrations of PFOA and PFOS increased with age in females reaching male levels at ages above 60 yr. Another novel finding was associated with the renal clearances of these chemicals, namely that the renal clearances of PFOA and PFOS were almost negligible in both sexes in human, in clear contrast to the large active excretion in other species such as female rats (Kudo et al., 2002). Even though such large active excretion of PFOA and PFOS was absent in monkeys, the renal clearances were still 300- to 1000-fold larger than those in human (Kudo and Kawashima, 2001). These two findings make us skeptical about the legitimacy of extrapolating animal data based on nominal dose-response curves to human risk assessment.

The age-dependent increases in PFOA and PFOS concentrations are not in accord with previous reports, which failed to find any age-dependent increases (Olsen et al., 2003a, 2003b, 2004a, 2004b; Harada et al., 2004b). This disagreement, however, can be explained at least by the following reasons. Olsen et al. (2003a, 2003b, 2004a) reported serum levels of PFOA and PFOS, however, did not evaluate the effects of geographical factors because they obtained blood samples from unidentified persons with uncertain residential histories. Second, we excluded regular blood donors from the present study, but they were not excluded from the study of Olsen et al. (2003a). Third, the present study covered a wide range of female age groups: some were menstruating while others were not. In contrast, our previous study (Harada et al., 2004b) and that of Olsen et al. (2004b) did not cover sufficient numbers of the two female populations. We thus

concluded that an experimental design that specified residential areas could reveal age- and sex-dependent changes in serum PFOA and PFOS levels, which would otherwise have been concealed by various confounding factors.

A study in rat revealed that hormone-regulated transporters such as *OAT2* and *OAT3* play pivotal roles in the renal clearance of PFOA (Kudo et al., 2002). Sex differences in renal excretion rates and renal clearances in monkeys suggest that hormone-regulated elimination is likely involved to a certain extent in this species (Kudo and Kawashima, 2001). Our study, however, did not suggest any evidence for sex hormone-regulated transport of these chemicals in human kidneys. One explanation would be to take plasma protein binding into account for the poor renal clearance (Han et al., 2003; Jones et al., 2003). This mechanism, however, is unlikely to explain the low renal excretion, which is specific to humans among primates. Hence, one might need to consider the mechanisms of the age-dependent increases in serum levels in females. One clue to answering this question would be to assume a sex-specific elimination route, and we therefore considered that menstrual bleeding might potentially be such a route for elimination in females. The elimination rates were comparable to renal excretion, suggesting that the rate of elimination in females with active menstrual cycles would be two-fold larger than that in males.

We tried to build a one-compartment pharmacokinetic model for PFOA and PFOS concentrations in serum incorporating sex specific route of elimination. The present one-compartment kinetic model could predict serum concentrations in both sexes at various ages fairly well. It is of particular interest that it could predict the increase in serum concentrations after menopause in females. Thane et al. (2002) observed a post-menarcheal-related decrease in serum inorganic lead, circumstantially supporting menstrual blood loss as a route of elimination. However, at present our model is immature. Our estimation of daily intakes was approximately 100 ng/day. This value is,

however, a simple mathematical estimation and thus needs validation by actual measurements. In addition, the model should incorporate elimination through feces as well as the effects of hormonal changes (Kudo et al., 2002), and alteration of binding affinity (Han et al., 2003; Jones et al., 2003). In the future, exposure levels in the diet and feces should be assessed; in particular, the latter route appears critical since enterohepatic circulation of these chemicals occurs (Johnson et al., 1984). More work is therefore needed to refine the model.

The present study has several other limitations. First, the sampling size was small. Subjects were recruited from a small community, thus there might have been a selection bias. In addition, a small number of female participants did not allow us to monitor changes in serum concentrations of PFOA and PFOS around menopause. Second, in Study 2, some elderly participants were taking medication during the study period, which might have changed the chemical disposition, metabolism, and protein binding. Third, renal clearances of PFOA and PFOS had large standard deviations but the reason was undetermined in this study. Other unexamined variables that affect renal clearances might have been present.

In conclusion, we found clear qualitative differences in renal excretion among species. Such differences seem to have a profound impact on the toxicokinetics of PFOA and PFOS. The differences were so remarkable that nominal doses in animal experiments cannot be surrogates for interpreting dose-response relationships. Alternatively, an internal dose approach using a simple but accurate pharmacokinetic model should be taken when animal data are extrapolated to humans, as proposed by Koizumi (1989, 1991).

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Figure legend

Figure. 1.

Relationships between age and serum concentrations of PFOA and PFOS in Kyoto city dwellers. The numbers of male and female participants were 20 and 28, respectively. The filled and open circles indicate females who were menstruating and who had been menopausal for more than 3 years, respectively. The solid lines show the values simulated with the one-compartment kinetic model, which was calculated using the half-lives in Table 5, and broken lines represent values calculated by changing $T_{1/2}$ by ±25%. In females, menstruation was assumed to stop at 50 yr of age.

Table legends

Table 1. Characteristics of participants in Study 1.

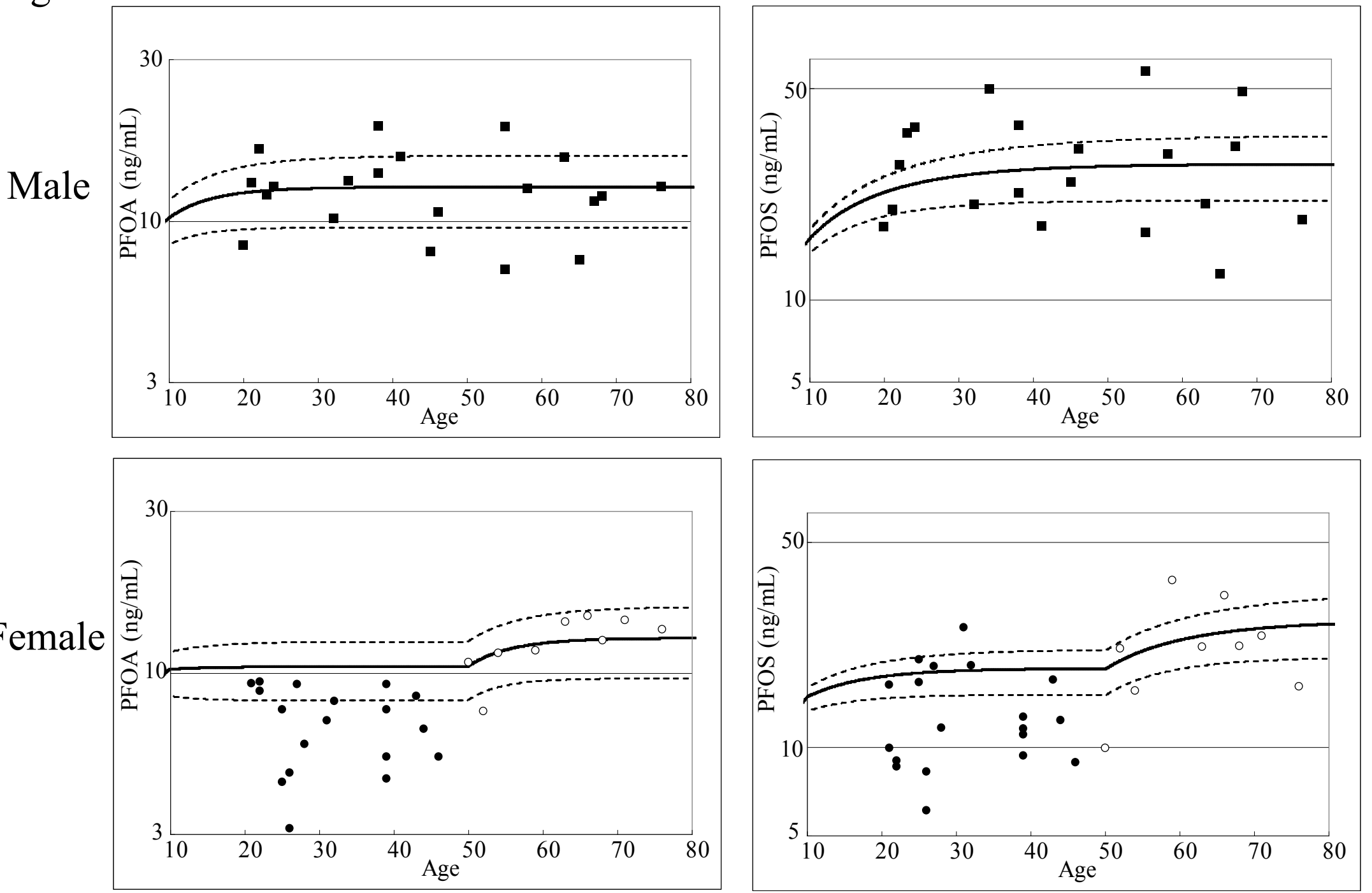
Table 2. Characteristics of participants in Study 2.

Table 3. Analysis of age and sex differences in PFOA and PFOS serum levels in Study 1.

Table 4. Concentrations and renal clearances of PFOA and PFOS in Study 2.

Table 5. Estimation of the toxicokinetic parameters of PFOA and PFOS in rat, monkey and human.

Fig. 1.



Open circle (○) : has been in menopause for more than 3 years.

Table 1
The study population of the Study 1

		Age (yrs)			
	No. of participants	Mean	SD[a]	Median	Range
Male	20	44.6	18.0	43	20-76
Female	28 (8)	41.2	16.9	39	21-76

A number in the brachet indicates a number of females in menopause.
a SD: Standard Deviation

Table 2
The study population of the Study 2

	Residential area[a]			Age	Height	Weight	Body surface area	GFR [b]
	Kyoto	Out of Kyoto		(yrs)	(cm)	(kg)	(m^2)	(mL/min)
Young Male (n=5)	1	4	Mean	21.6	166.0	60.0	1.66	121.0
			SD[c]	0.9	4.4	6.7	0.11	7.1
Young Female (n=5)	3	2	Mean	23.0	158.4	48.2	1.46	95.3
			SD[c]	2.8	4.2	7.1	0.12	14.1
Old Male (n=5)	5	0	Mean	67.8	161.2	62.2	1.65	87.9
			SD[c]	5.0	4.0	9.9	0.13	11.1
Old Female (n=5)	5	0	Mean	68.8	149.2	48.4	1.41	96.5
			SD[c]	5.0	6.9	5.9	0.13	15.6
total (n=20)	14	6	Mean	45.3	158.7	54.7	1.55	100.2
			SD[c]	23.9	17.1	7.8	0.16	9.6

a 'Kyoto' indicates Kyoto city dweller. 'Out of Kyoto' indicates those who recently moved to the Kyoto city from other districts outside Kinki.
b GFR: Glomerular Filtration Rate
c SD: Standard Deviation

Table 3
Effects of age class and sex differences on serum levels in Study 1

PFOA	Male			Female			Difference by sex
Age class	No.	Mean(ng/ml)	SD[a]	No.	Mean(ng/ml)	SD[a]	p value
20-50 yrs	12	12.96	3.43	20[b]	7.89	3.61	0.0005
51 yrs -	8	12.41	4.09	8[c]	12.63	2.42	0.9011
Difference by age class	p value	0.75		p value	0.0022		n.s.

PFOS	Male			Female			Difference by sex
Age class	No.	Mean(ng/ml)	SD[a]	No.	Mean(ng/ml)	SD[a]	p value
20-50 yrs	12	28.28	10.19	20[b]	13.18	5.03	0.0001>
51 yrs -	8	29.44	16.44	8[c]	24.00	7.55	0.409
Difference by age class	p value	0.85		p value	0.0001		n.s.

Two-way ANOVA showed no interaction between age class and sex. n.s.: not significant
a SD: Standard Deviation
b All subjects had menstrual cycles.
c All subjects did not have menstrual cycles.

Table 4
Concentrations and renal clearances of PFOA and PFOS in Study 2

	NO	Residential area[a] Kyoto city dweller		Serum (ng/mL) PFOA	PFOS	Urine (ng/day) PFOA	PFOS	Renal clearance (mL/day) PFOA	PFOS
Young Male	1	YES		13.2	19.4	20.4	4.6	1.55	0.24
	2	NO		7.6	9.0	25.3	9.6	3.33	1.07
	3	NO		7.0	12.6	8.7	8.6	1.24	0.68
	4	NO		5.2	9.2	12.0	10.9	2.30	1.19
	5	NO		6.6	12.8	14.5	1.6	2.20	0.13
			Mean	7.9	12.6	16.2	7.1	2.12	0.66
			SD[b]	3.1	4.2	6.7	3.9	0.80	0.48
Young Female	1	YES		8.8	9.0	9.8	5.5	1.12	0.61
	2	YES		20.6	16.4	22.0	24.8	1.07	1.51
	3	YES		9.4	8.6	9.9	10.8	1.06	1.25
	4	NO		10.8	12.6	8.8	1.4	0.81	0.11
	5	NO		7.6	9.4	12.9	10.2	1.70	1.09
			Mean	11.4	11.2	12.7	10.5	1.15	0.91
			SD[b]	5.2	3.3	5.4	8.9	0.33	0.56
Old Male	1	YES		12.8	18.0	39.0	6.0	3.05	0.33
	2	YES		11.6	32.0	34.8	36.2	3.00	1.13
	3	YES		7.6	11.8	12.9	14.9	1.70	1.27
	4	YES		15.8	20.4	13.3	8.0	0.84	0.39
	5	YES		12.0	49.2	9.0	5.5	0.75	0.11
			Mean	12.0	26.3	21.8	14.1	1.87	0.65
			SD[b]	2.9	14.8	14.0	12.9	1.12	0.52
Old Female	1	YES		13.6	16.2	15.4	8.7	1.13	0.53
	2	YES		15.0	33.0	19.1	29.7	1.27	0.90
	3	YES		14.4	22.0	20.2	21.0	1.40	0.96
	4	YES		12.6	22.2	16.8	23.1	1.33	1.04
	5	YES		14.6	24.0	27.7	24.5	1.90	1.02
			Mean	14.0	23.5	19.8	21.4	1.41	0.89
			SD[b]	1.0	6.1	4.8	7.8	0.29	0.21

a 'YES' indicates Kyoto city dweller. 'NO' indicates those who recently moved to the Kyoto city from other districts outside Kinki.
b SD: Standard Deviation

Table 5
Estimation of toxicokinetic parameters of PFOA and PFOS in rats, monkeys and humans

			Serum half-life	Total Clearance(1)	Renal Clearance(2)		Menstrual bleeding (3) [e]	Proportion of (2) or (3) to (1)	
			(day)	CL_{tot} (mL/day/kg)	CL_R (mL/day/kg)	(2)/GFR (%)	(mL/month/kg)	(2)/(1) (%)	(3)/(1) (%)
PFOA	Wistar rat [a]	male	5.63	50.4	46.1	0.38	-	91.4	-
		female	0.08	2233.4	1054.1	8.61	-	47.2	-
	Japanese macaque [b]	male	5.6	37.1	15	0.38	-	40.4	-
		female	2.7	77.0	32	0.80	-	41.5	-
	human [c]	male (61kg)	1573	0.132	0.033	1.06×10^{-3}	-	25.1	-
		female (48kg)			0.027	0.76×10^{-3}	0.87	20.7	23.6
PFOS	Cynomolgus monkey [d]	male	200	1.081	-				
	human [c]	male (61kg)	3165	0.066	0.012	3.69×10^{-4}	-	17.5	-
		female (48kg)			0.019	5.20×10^{-4}	0.87	28.5	47.6

GFR: glomerular filtration rate

a Half-lives, total and renal clearance were reported by Kudo et al. (2002)

b Half-lives and renal clearance were reported by Kudo and Kawashima (2001). Total clearance were calculated from the volume distribution V. V was calculated as 300 ml/kg.

c Half-lives in retired workers were reported by Burris et al. (2002). Total clearance were calculated from the volume distribution V. V was calculated as 300 ml/kg. The means of renal clearance in Study 2 participants were presented.

d Half-life was reported by Seacat et al. (2002), and total clearance was calculated as previously reported (Harada et al., 2003).

e Menstrual serum loss was assumed to 42 mL/month (Hallberg et al., 1966).