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The influence of time, sex and geographic factors on levels of perfluorooctane sulfonate and perfluorooctanoate in human serum over the last 25 years

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Abstract:

Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are important perfluorochemicals (PFCs) in various applications. Recently, it has been shown that these chemicals are widespread in the environment, wildlife and humans. But the kinds of factors that affect their levels in serum are unclear, and it is also not clear whether exposure to them is increasing or not. To investigate the impacts of time, geographical location and sex on the levels of these chemicals, we measured PFOS and PFOA concentrations in human sera samples collected both historically and recently in Miyagi, Akita and Kyoto Prefectures in Japan. The PFOS and PFOA levels in sera [Geometric Mean (Geometric Standard Deviation)](μg/L) in 2003 ranged from 3.5(2.9) in Miyagi to 28.1(1.5) in Kyoto for PFOS and from 2.8(1.5) to 12.4(1.4) for PFOA. Historical samples collected from females demonstrated that PFOS and PFOA concentrations have increased by factors of 3 and 14, respectively, over the past 25 years. There are large sex differences in PFOS and PFOA concentrations in serum at all locations. Furthermore, there are predominant regional differences for both PFOS and PFOA concentrations. In Kyoto the concentrations of PFOA in dwellers who had lived in the Kinki area for more than 10 years were significantly higher than in

people who had recently moved into the area, in both sexes. This finding suggests that there are sources of PFOA in the Kinki area that have raised the PFOA serum levels of its inhabitants. Further studies are needed to elucidate these sources in the Kinki area of Japan.

Key words
Perfluorooctane sulfonate, perfluorooctanoate, serum, exposure, geographic analysis, sex differences, long-term trend

Introduction

Perfluorinated alkyl compounds, of which representative chemicals include perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), are a class of specialty chemicals used in a variety of applications, such as in lubricants, paints, cosmetics, and fire-fighting foams[1-3]. PFOS has been an important perfluorinated surfactant, but recently, in 2002, after 50 years of production, 3M has phased out its manufacture[4]. These chemicals are regulated by various governments.

PFOS has been shown to be found globally in a variety of living organisms, including humans[5] and wildlife[6]. Worldwide distribution of PFOS has been attributed to its resistance to degradation in ecological systems[3] and its bioconcentration[7]. There is a large difference between the distributions of PFOA and PFOS. PFOA is only detected in selected areas[8, 9].

There have been several studies on PFOS and PFOA levels in human serum[5, 10, 11]. Data from these studies suggest that PFOS levels in human serum are about 10-50 μg/L for PFOS and 1-10 μg/L for PFOA. There is circumstantial evidence that gender differences and geographic factors may be modifiers for human serum levels[12-14], although demographic features, life styles and residential histories of serum donors are not reported. A commonly accepted speculation is that PFOS serum levels have not changed over the past 30 years[5, 15]. On the other hand, there is a report that workers in a fluorochemical manufacturing plant were exposed to PFCs. Geometric means of serum concentrations of PFOA and PFOS were 941 μg/L and 899 μg/L respectively[16].It has recently been suggested that PFOS and related compounds are human and animal carcinogens[17-19]. Although hazard identification is still at a premature stage, some observations on workers suggest the possibility that PFOS may be associated with bladder cancer mortalities[19]. Other lines of evidence generated by animal studies suggest that PFOS induces liver tumors[17].

We previously reported that concentrations of PFOS and PFOA in drinking water in the Kinki area were several times higher than in other areas in Japan, as well as those in surface water[20]. It is, therefore, possible that their levels in the serum of residents in the Kinki area may be higher than those in other

areas.

The major aim of the present study was to evaluate the long-term levels of PFOS and PFOA in human serum in the general public using both historical and recent samples, in parallel with the evaluation of sex and geographic factors. The study was also designed to systematically evaluate factors affecting serum levels of PFOS and PFOA. The present study is expected to provide background data for biological monitoring in workers who are exposed to these organofluorine chemicals as well as in the general population.

Methods and Materials

Experimental design

To evaluate a long-term trend in blood concentration levels of PFOS and PFOA, blood samples which were collected about 25 years and 10 years ago were an obligatory requirement. Samples collected in Yokote (the middle part of Akita) and Taiwacho (the northern part of Miyagi) were only accessible to us for the present study. We thus chose to use sets of samples.

To evaluate possible geographic differences at the present time, we compared samples collected in three geographic areas: Kyoto, Akita and Miyagi. The rationale for the selection of these areas was based on our previous report that concentrations of PFOA and PFOS in drinking water is reported to be higher in Kyoto than at the two other sites [20]. We thus expected to test

whether higher drinking water levels may be associated with increased PFOA and PFOS in serum.

Population

Recent serum samples were collected from participants living in Kyoto, Akita (and Miyagi in 2003. Workers in fluorochemical manufacturing factories were not included in the participants. A 4 ml blood sample was donated by each person. When these samples were collected, participants were interviewed as to their age, sex, smoking status (Current smoker, exsmoker or never a smoker) and residential history. Serum was separated from the RBC and other cellular components and then stored in a refrigerator at –20^{o}C.

Historical serum samples that were collected in 1995 and 1991 in Yokote city, Akita Japan (simply Akita hereafter). Blood donors were either farmers or hospital workers. These samples were originally collected for the purpose of monitoring serum DDT and DDE levels. Another set of blood samples were collected in Taiwacho, Miyagi in 1977 and were donated by females from farming households (simply Miyagi hereafter). These serum samples were originally collected for the purpose of monitoring serum ion levels.

Age, gender, smoking status and residential histories of donors were recorded when the serum samples were collected. Blood samples had been stored at –20^{o}C after separation.

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 the PFOS and the PFOA used as standards were greater than 98%. We did not correct the reported concentrations according to purity.

PFOS and PFOA extraction in serum

We employed the extraction process developed by Hansen[5)]. 0.4 mL of sera, 1 mL of 0.5 M TBA solution, and 2 mL of 0.25 M sodium carbonate buffer were added to a 15-mL polypropylene tube for extraction, and mixed. 5 mL of methyl tertiary-butyl ether (MTBE) was added to the solution, the organic and aqueous layers were separated by centrifugation, and the former was removed from the solution. The aqueous mixture was rinsed with MTBE and separated twice. The solvent was evaporated at room temperature under a nitrogen 1 mL/min gas flow, and the sample was reconstituted in 0.5 mL of methanol. The samples were then passed through a filter (Whatman AUTOVIAL R5)(Whatman Japan, Tokyo).

Instrumental analysis

The solution was then analyzed by LC/MS as previously reported[20, 21]. The lowest limits of detection (LOD) (μg/L) were 0.06 for PFOA and 0.04 for PFOS in the serum samples. The lowest limits of quantification (LOQ) (μg/L) were 0.1 for both analytes in the serum samples.

Ethical issues

Blood samples collected in 2003 were taken after formal informed consent had been obtained. In the historical samples, verbal informed consent was obtained when the blood samples were donated. The research protocol was reviewed and approved by the ethical committee of Kyoto University.

Statistics

For statistical analysis, we grouped ages into three categories: younger than or equal to 30 years, between 31 and 50 and older than 50.

Statistical analyses were conducted after logarithmic transformation. The differences between means were tested by multiple ways ANOVA or Student's t test when appropriate. $P<0.05$ was considered to be significant. All statistical analyses were carried out with SAS software[22]. Samples that were under the

LOQ were assigned a value of 0.1 (μg/L).

Results

Study population

The number of participants in each residential area, and the mean ages and smoking status are summarized in Table 1.

In Kyoto, 34 participants (n=34: 14 males and 20 females) had lived in the Kinki area (Hyogo, Osaka, Wakayama, Nara, Kyoto and Shiga) for at least 10 years (Fig. 1) (referred to as Kinki dwellers, hereafter). The remaining 20 (14 males and 6 females) had moved into the Kinki district from other districts within the previous 6 months to 2 years (referred to as movers, hereafter). In contrast, participants in Akita (82 males and 110 females) and Miyagi (32 males and 62 females) had lived in the same areas without moving.

In Kyoto, most of the participants (both male and female) were nonsmokers. In other areas, most female participants were nonsmokers.

PFOS and PFOA concentrations in 2003

The serum levels of PFOA and PFOS in Akita samples are shown in Fig.2. For Miyagi samples, skewed patterns were also observed (data not shown). For Kinki dwellers, due to the small sizes, skewness was not apparent. Values were logarithmically

transformed in this study.

There were significant geographic differences in PFOA and PFOS serum concentrations between samples collected in Kyoto, Akita and Miyagi, both for males and females (Table 2).

The geometric means of serum PFOS concentrations were significantly higher in males than females for all samples collected in 2003 (Table 2). In addition, PFOA serum concentrations in males were significantly higher than those in females for Kyoto and Akita samples collected in 2003. Age class and smoking status did not influence the PFOA or PFOS serum levels in males from either Miyagi or Akita (data not shown). In nonsmoking females from Miyagi and Akita, age did not affect the levels (data not shown). In Kyoto samples, we also evaluated the effects of age class on serum PFOS or PFOA levels in Kinki dwellers. Age did not have any influence on the serum levels (data not shown).

Since it has been reported that environmental contamination levels of PFOS and PFOA are the most intensive in the Kinki district[20], we compared the PFOS and PFOA serum levels in Kinki dwellers and movers. For males, the serum levels of PFOS and PFOA were significantly greater in the Kinki dwellers than in the movers (Table 3). For females, PFOA levels in Kinki dwellers were significantly greater than in the movers, but PFOS levels were only marginally greater (Table 3).

Long-term serum concentrations of PFOS and PFOA

Concentrations of PFOS and PFOA in serum collected in 2003, 1995, 1991 and 1977 are shown in Table 4. Between 1977 and 2003, sample serum concentrations in Miyagi increased by a factor of 3 for PFOS, and a factor of 14 for PFOA. In Akita, concentrations of PFOA increased significantly between 1995 and 2003. In contrast, PFOS concentrations in the Akita samples did not show any evidence of a concentration increase from 1991 to 2003, for either sex.

Discussion

In the present study, we have shown that serum levels of PFOS and PFOA are influenced by several factors. The present study is the first report to systematically investigate the determining factors for serum levels of PFOS and PFOA. Sex and residential area are the most influential factors, while age and smoking status are not as influential.

In terms of geographic differences, it should be noted that PFOS and PFOA serum levels in males are significantly higher in Kinki dwellers than in other residents. This was also found to be the case for PFOA levels in females. It is also interesting to note that serum levels of PFOS and PFOA in movers all fell somewhere between those of the Kinki dwellers and those of

participants from Akita or Miyagi. This finding is in agreement with our previous observation that environmental PFOS and PFOA contamination is more intense in the Kinki district than in other districts[20]. Additionally, it was suggested that drinking water contamination might affect the PFOS serum level to some extent[20, 23, 24]. More works need to be done in order to find the sources of contamination in the Kinki district.

Serum levels of PFOS and PFOA of the Kinki dwellers were close to those of samples collected from several biological supply companies in the United States[5], but human exposure to PFOA and PFOS seemed to be much lower in the Tohoku district than in the U.S. at the present time.

In the present study, we used historical samples, as these may give us an insight into the long-term human exposure trend. It was shown that PFOS levels reached a plateau in the mid 1990s, based on the data collected in Akita. In contrast, results from both Akita and Miyagi showed that PFOA concentrations are steadily increasing, suggesting the possibility that in the northern part of Japan environmental PFOA contamination is still increasing, while PFOS levels may have reached a steady state. The increasing trend in serum levels of PFOA may be correlated with the trend in industrial activities in Japan.

This study has several limitations. First, to evaluate a long-term trend, scarcity of samples posed restrictions on

geographical selections and the numbers of samples available: In fact, we could not collect historical samples in the Kinki district. Thus the present data do not represent serum levels of PFOA and PFOS in modern Japanese in any sense. Simple extrapolation of the observed long-term trends in Miyagi and Akita to the long-term trends in other areas in Japan is misleading. This argument is also applicable to the interpretation of geographical differences. Obviously more studies need to be done to validate our findings. A second limitation is associated with the uncertainty of sources of exposure to PFOA and PFOS in Japan. This caveat, however, is not specific to our study. This study rather provided pieces of evidence, as yet circumstantial, that drinking water might be one of the major sources of the human body burden.

In conclusion, we found that human exposure to both PFOS and PFOA was more intensive in the Kinki district than in the other areas studied. Work needs to be done to find the sources of human exposure to these compounds in the Kinki area, as well as to determine the long-term exposure trends.

Acknowledgments:

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Tables

Table 1. Study population

Sampling site	Time	Male	female
Kyoto	2003		
	No. of participants	28	26
	Age	36.6±11.7	37.1±10.9
	Residential period		
	>=10y	14	20
	2y-6mo	14	6
	Smoking		
	Never	23	25
	Current	3	1
	Ex	2	0
Miyagi	2003		
	No. of participants	32	23
	Age	40.3±12.2	41.6±12.5
	Smoking		
	Never	9	18
	Current	23	5
	Ex	0	0
	1977		
	No. of participants	-	39
	Age	-	47.2±6.4
	Smoking		
	Never	-	39
	Current	-	0
	Ex	-	0
Akita	2003		
	No. of participants	66	50
	Age	41.3±12.5	33.5±12.2
	Smoking		
	Never	25	38
	Current	38	10
	Ex	3	2
	1995		
	No. of participants	-	40
	Age	-	36.3±2.6
	Smoking		
	Never	-	40
	Current	-	0
	Ex	-	0
	1991		
	No. of participants	16	60
	Age	32.2±11.7	34.5±7.2
	Smoking		
	Never	3	60
	Current	13	0
	Ex	0	0

Values for Age are mean ± standard deviation.

Table 2 . Geographic differnces in serum concentration of PFOS and PFOA in 2003

	Male				Female				Sex difference
Sampling site	No.	GM	GSD	ANOVA	No.	GM	GSD	ANOVA	t-test
	PFOS (μg/L)								p value
Kyoto	14	28.1	1.5	A	20	13.8	1.5	A	<0.01
Akita	66	12.9	1.5	B	50	6.9	1.4	B	<0.01
Miyagi	32	5.7	1.8	C	23	3.5	2.9	C	<0.05
	PFOA (μg/L)								
Kyoto	14	12.4	1.4	A	20	7.1	1.4	A	<0.01
Akita	66	3.4	1.5	B	50	2.5	1.6	B	<0.01
Miyagi	32	3.3	2.0	B	23	2.8	1.5	B	

ANOVA: Different letters indicate that their corresponding values are statistically different (P<0.001).
t-test: student's t-tset between Male and Female
No.:Number of participants; GM: Geometric Mean; GSD: Geometric Standard Deviation

Table 3. PFOS and PFOA levels in sera in Kyoto samples

	Male			Female		
Origin	Kinki [a]	Other [b]	p value [c]	Kinki [a]	Other [b]	p value [c]
No. of participants	14	14		20	6	
PFOS (μg/L)						
GM	28.1	21.8	<0.01	13.8	9.4	0.053
GSD	1.5	1.7		1.5	1.3	
PFOA (μg/L)						
GM	12.4	7.1	<0.01	7.1	3.7	<0.01
GSD	1.4	1.4		1.5	1.3	

a) Lived in the Kinki area for at least 10 years
b) Had moved into the Kinki area within the previous 6 months to 2 years
c) student's t-test between Kinki and Other

Table 4. Long-term exposure trend of serum PFOA and PFOA

		Male					Female				
		PFOS (μg／L)		PFOA (μg／L)			PFOS (μg／L)		PFOA (μg／L)		
Sampling site	Date	GM	GSD	GM	GSD	No.	GM	GSD	GM	GSD	No.
Miyagi	2003	5.7	2.0	3.3	2.0	32	3.5	2.9	2.8	1.5	23
	1977	-	-	-	-	-	1.1	1.8	0.2	2.0	39
	p value	-		-			<0.001		<0.001		
Akita	2003	12.9	1.5	3.4	1.5	66	6.9^{A}	1.4	2.5^{A}	1.6	50
	1995	-	-	-	-	-	8.7^{B}	1.3	1.9^{B}	1.4	40
	1991	10.2	1.5	2.2	1.4	16	7.9^{A}	1.4	1.8^{B}	1.5	60
	p value			<0.001			$<0.05^{\#}$		$<0.05^{\#}$		

ANOVA: Different letters indicate that their corresponding values are statistically different.

Figure captions

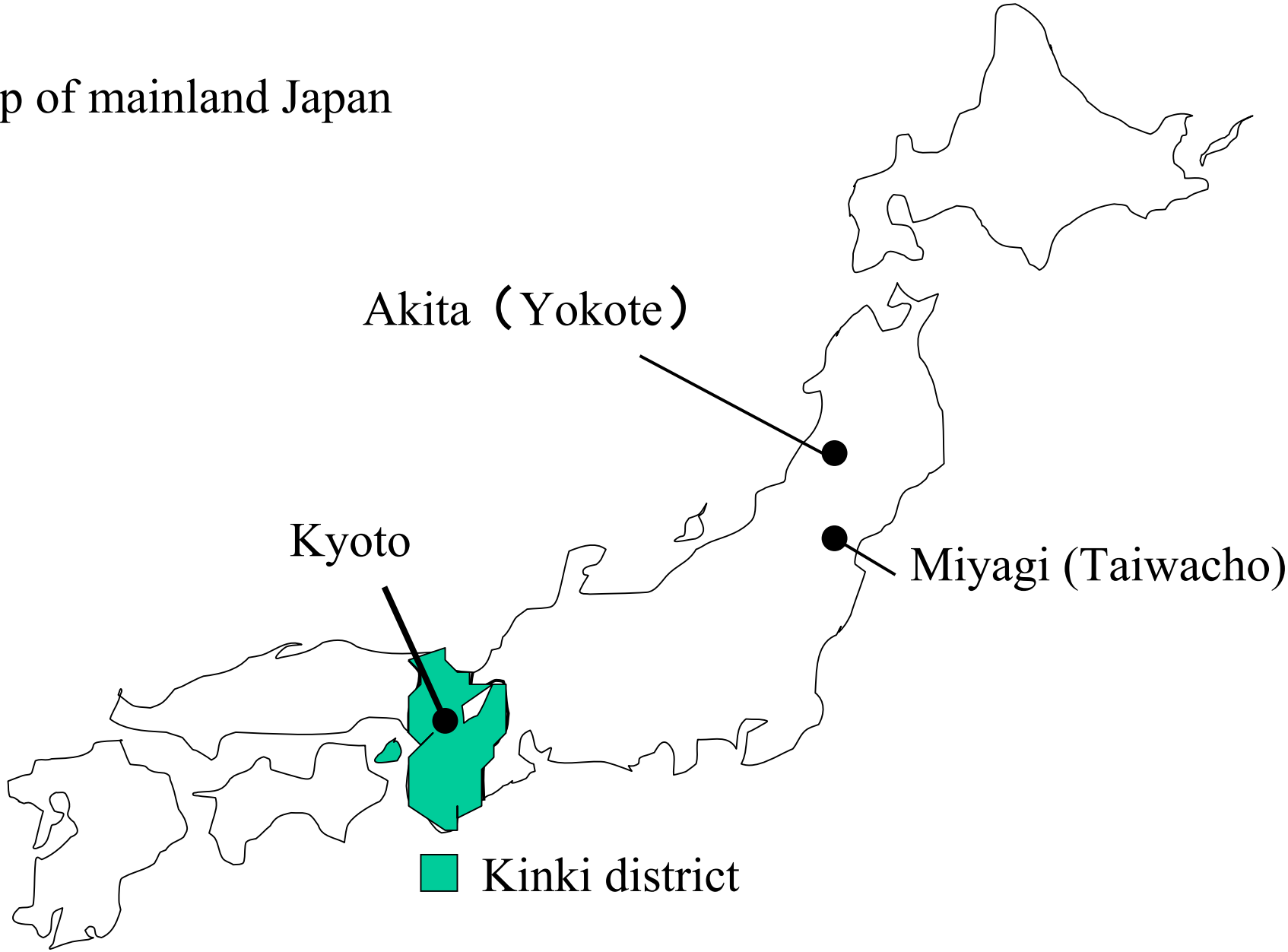
Fig. 1.

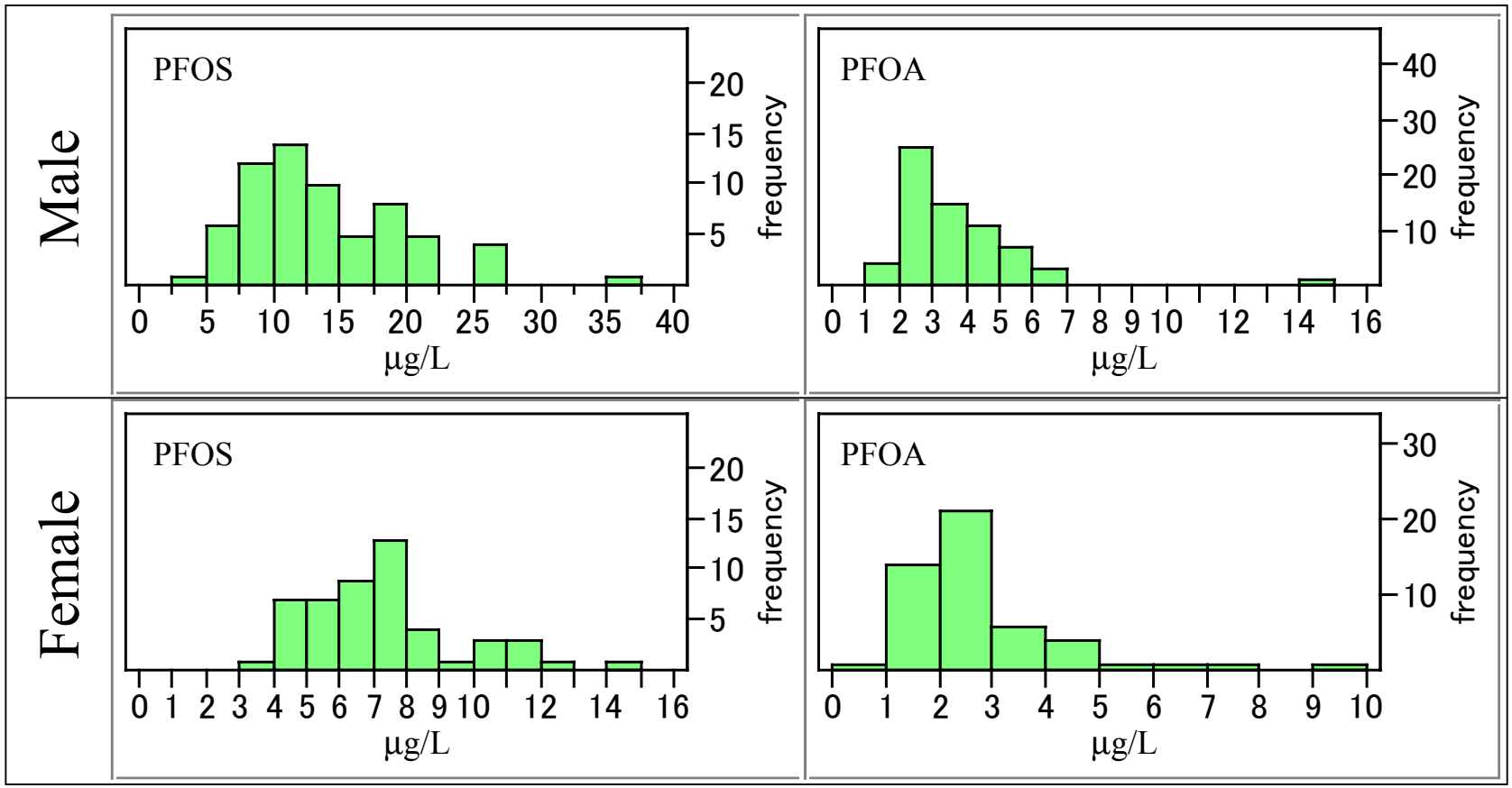
Serum sampling sites in Japan, and boundary of Kinki district.

Fig. 2.

Distribution of serum values in 2003 residents in Akita (82 males and 110 females).

Map of mainland Japan




Male
PFOS
frequency
0 5 10 15 20 25 30 35 40
µg/L
PFOA
frequency
0 1 2 3 4 5 6 7 8 9 10 12 14 16
µg/L
Female
PFOS
frequency
0 1 2 3 4 5 6 7 8 9 10 12 14 16
µg/L
PFOA
frequency
0 1 2 3 4 5 6 7 8 9 10
µg/L

・表題

過去 25 年間にわたるヒト血清中ペルフルオロオクタンスルホン酸・ペルフルオロオクタン酸濃度に及ぼす、時間、性、地理的要因の影響

・著者名

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・要旨

ペルフルオロオクタンスルホン酸 perfluorooctanesulfonate（PFOS）と ペルフルオロオクタン酸 perfluorooctanoate（PFOA）は種々の用途で重要なペルフルオロ化合物の一つである。 最近、これらの化学物質が環境、野生生物とヒトの広範囲にわたる汚染を引き起こしていることが示された。しかしながら、血清中 PFOS・PFOA 濃度に影響を与える要因は明確でなく、現在それらの曝露が増加しているかどうかは同じく明確ではない。 これらの化学物質のレベルに対する時間、地域、性別の影響を調査するために、我々は日本国内で宮城、秋田と京都で血清試料を過去と現代にわたって集めた。血清中 PFOS と PFOA 濃度を LC/MS により測定した。血清中 PFOS・PFOA 濃度［幾何平均（幾何標準偏差)］(μg/Ｌ）は、2003 年において PFOS について、宮城の 3.5（2.9）から京都の 28.1（1.5）まで、PFOA についても、宮城の 2.8（1.5）から京都の 12.4（1.4）までの範囲を示した。女性から集められた過去の血清試料により、PFOS・PFOA 濃度がこれまでの 25 年にわたって、それぞれ、3、14 倍に増加したことを明示した。また、すべての地域内で血清中 PFOS・PFOA 濃度に大きな性差があった。さらに、PFOS・PFOA 濃度両方について地域間で顕著な相違があった。京都において、10 年以上、近畿地区に居住していた住民の PFOA 濃度は、最近その区域に引っ越してきて、半年以上 2 年未満経過した人々で、両方の性で、有意に高かった。この結果は住民の血清中 PFOA 濃度を高めうる PFOA の汚染源が近畿地区にあることを示唆する。さらなる研究がこれらの近畿地区の汚染源を説明するために必要である。