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Dioxin Concentration in the Blood of Patients Collected during Medical Check-up for Yusho in 2004-2005

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Abstract We measured the concentrations of polychlorinated dizenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and non-*ortho* coplanar polychlorinated biphenyls (non-*ortho* PCBs) in blood collected from 242 Yusho patients and 74 Yusho-suspected persons in 2004 and 237 Yusho patients and 114 Yusho-suspected persons in 2005. The sums of toxic equivalents (TEQ) concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho patients in 2004 and 2005 were 126.1 and 124.2 pg TEQ/g lipid, respectively, and the concentrations were 3.4 and 3.3 times higher than those of normal controls that had been previously reported, respectively. Those of the Yusho-suspected persons were about 0.8 and 1.0 times higher than those of normal controls, respectively. Although the TEQ concentrations of PCDDs and non-*ortho* PCBs among Yusho patients, Yusho-suspected persons, and normal controls were nearly the same, the PCDFs levels of Yusho patients were about 9.8 and 9.5 times higher than those of normal controls in 2004 and 2005, respectively. The concentration of 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PeCDF), which was the highest among PCDFs congeners for Yusho patients, was about 10.6 and 10.2 times higher than that of the normal controls in 2004 and 2005, respectively. In the case of Yusho-suspected persons, the concentrations were 0.9 and 1.4 times higher than those of normal controls, respectively. However, some of the Yusho-suspected persons showed a high concentration of 2,3,4,7,8-PeCDF that was approximately 15 times greater than concentrations in normal controls. Of 74 Yusho-suspected persons measured in 2004, 7 persons were officially registered as Yusho patients based on the "New Diagnostic Criteria" that officially became the diagnostic criteria for Yusho exposure on September 29, 2004, which included a concentration of 2,3,4,7,8-PeCDF in the blood, and in 2005, 14 persons of 114 Yusho-suspected persons were officially registered as Yusho patients.

Introduction

In 1968, over 1800 persons in western Japan developed a strange skin disease, later named Yusho disease, which found to have been caused by the ingestion of rice bran oil contaminated with polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated quarterphenyls (PCQs), and polychlorinated terphenyls (PCTs)[1]. Over 36 years have passed since the Yusho outbreak, and although almost all of the typical symptoms affecting Yusho patients have improved, some patients are still afflicted with subjective symptoms. From the results of extensive

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research by the Yusho study group investigating this disease, PCDFs were concluded to be the primary cause of Yusho disease symptoms[1]. However, the concentrations of PCDFs in the blood were not included in the diagnostic criteria because the amount of blood that can be collected from Yusho patients is restricted, and thus there were practical difficulties involved in measuring these concentrations. Recently, however, the measurement of PCDDs, PCDFs, and non-*ortho* PCBs in blood has become possible using small amounts of blood collected from participants in an annual medical check-up for Yusho patients[2)3)]. We measured the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in blood samples collected from 78 Yusho patients living in Fukuoka Prefecture in 2001 for a preliminary study[4]. Moreover, we measured the concentrations of these dioxin-like compounds in blood samples collected from 279 Yusho patients and 92 Yusho-suspected persons living in Japan in 2002 and 269 Yusho patients and 74 Yusho-suspected persons living in Japan in 2003, and we also measured the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of 127 normal controls unaffected by Yusho living in Fukuoka Prefecture whose ages were similar to those of the Yusho patients[5)~7)]. The results showed that PCDFs in the blood of Yusho patients, in particular 2,3,4,7,8-PeCDF, are still present at a much higher concentration than in the blood of unaffected people more than 35 years after the Yusho incident. Therefore, 2,3,4,7,8-PeCDF was indicated to be the most important compound for the establishment of new diagnostic criteria for Yusho disease[5)~7)]. To establish the new criteria, however, it has been necessary to measure the PCDFs concentration in the blood of many more patients and to statistically analyze the relationship between the concentration levels and clinical symptoms.

In this study, we measured the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in blood collected from 242 Yusho patients and 74 Yusho-suspected persons in 2004 and 237 Yusho patients and 114 Yusho-suspected persons in 2005, and compared with concentrations of these dioxin-like compounds among the groups of Yusho patients, Yusho-suspected persons, and normal controls that had been previously reported.

Materials and Methods

1. Sampling

Medical check-up for Yusho patients have been conducted annually to determine their health status since the outbreak of Yusho incident[1]. The medical check-up is open not only to those persons officially registered as Yusho patients but also to Yusho-suspected persons who regard themselves as potential victims[8]. Both officially registered Yusho patients and Yusho-suspected persons are examined based on the "Diagnostic Criteria for Yusho"[1)8)]. The blood samples examined in this study were collected from 316 and 351 participants, each of whom received a medical check-up in 2004-2005, and each of whom gave his or her informed consent to participate in this study. The 316 participants were 242 Yusho patients and 74 Yusho-suspected persons in 2004, and the 351 participants were 237 Yusho patients and 114 Yusho-suspected persons in 2005. Blood samples of 10 ml were collected using a vacuum blood-collecting tube containing heparin and were stored at 4°C until analyses for concentrations of PCDDs, PCDFs, and non-*ortho* PCBs.

2. Materials

Native PCDDs, native PCDFs, and native non-*ortho* PCBs, as authentic standards, were purchased from Wellington Laboratories (Ontario, Canada). [$^{13}C_{12}$]-PCDDs, [$^{13}C_{12}$]-PCDFs, and [$^{13}C_{12}$]-non-*ortho* PCBs, as internal standards, were also purchased from Wellington Laboratories. An active carbon column was prepared as follows: active carbon was purchased from Nacalai Tesque (Kyoto, Japan), refluxed 3 times with toluene for 1 hour, and dried in vacuum, after which 500 mg of the active carbon was mixed with 500 g of anhydrous sodium sulfate (Wako Pure Chemical Industries, Ltd., Tokyo, Japan). A silver nitrate / silica gel was purchased from Wako Pure Chemical Industries, Ltd. All reagents and solvents used in this experiment were of the analytic grade of dioxin that is commercially available.

3. Analysis of PCDDs, PCDFs , and non-*ortho* PCBs

The extraction of PCDDs, PCDFs, and non-*ortho* PCBs from the blood was performed using a previously reported method[2)3)]. Concentrations of the PCDDs, PCDFs, and non-*ortho* PCBs were measured using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC / HRMS) equipped with a solvent cut large-volume injection system (SGE Ltd., Victoria, Australia)[2)3)]. The analytic conditions were as follows: the gas chromatograph was an HP-6890A (Agilent Technologies Inc., California, USA) equipped with an Autospec Ultima NT, (Micromass Ltd., Manchester, UK) and an SCLV injection system; the column used was a BPX-5 fused silica pre-capillary column, 0.25 mm i.d.×6 m, 0.25 μm film thickness (SGE Ltd.); the analytic column (BPX-Dioxin I) was 0.15 mm i.d.× 30 m (SGE Ltd.); the column was heated from 160°C to 300°C at a rate of 20°C / minute, maintained at 300°C for 12 minutes, cooled to 195°C at a rate of 70°C / minute, maintained at 195°C for 1 minute, heated to 300°C at a rate of 3°C / minute. The injection temperature and ion source temperature were both maintained at 280°C, and the carrier gas (helium) flow rate (constant flow) was 1.3 ml / minute. The ionizing current, ionizing energy, accelerating voltage, and trap current were 750 μA, 40 eV, 8.0 kV and 750 μA, respectively. PCDDs, PCDFs, and non-*ortho* PCBs were analyzed in a single-ion record mode. The resolution was maintained at 10,000 at 5% valley. For the analysis of tetrachlorodibenzo-*p*-dioxin (TCDD), pentachlorodibenzo-*p*-dioxin (PeCDD), hexachlorodibenzo-*p*-dioxin (HxCDD), heptachlorodibenzo-*p*-dioxin (HpCDD), and octachlorodibenzo-*p*-dioxin (OCDD), we used [$^{13}C_{12}$]-2,3,7,8-TCDD, [$^{13}C_{12}$]-1,2,3,7,8-PeCDD, [$^{13}C_{12}$]-1,2,3,4,7,8-HxCDD, [$^{13}C_{12}$]-1,2,3,6,7,8-HxCDD, [$^{13}C_{12}$]-1,2,3,7,8,9-HxCDD, [$^{13}C_{12}$]-1,2,3,4,6,7,8-HpCDD, and [$^{13}C_{12}$]-1,2,3,4,6,7,8,9- OCDD as internal standards, respectively. For the analysis of tetrachlorodibenzofuran (TCDF), pentachlorodibenzofuran (PeCDF), hexachlorodibenzofuran (HxCDF), heptachlorodibenzofuran (HpCDF), and octachlorodibenzofuran (OCDF), we used [$^{13}C_{12}$]-2,3,7,8-TCDF, [$^{13}C_{12}$]-1,2,3,7,8-PeCDF, [$^{13}C_{12}$]-2,3,4,7,8-PeCDF, [$^{13}C_{12}$]-1,2,3,4,7,8- HxCDF, [$^{13}C_{12}$]-1,2,3,6,7,8-HxCDF, [$^{13}C_{12}$]- 1,2,3,7,8,9-HxCDF, [$^{13}C_{12}$]-2,3,4,6,7,8- HxCDF, [$^{13}C_{12}$]-1,2,3,4,6,7,8-HpCDF, [$^{13}C_{12}$]- 1,2,3,4,7,8,9-HpCDF, and [$^{13}C_{12}$]-1,2,3,4,6,7,8,9-OCDF as internal standards, respectively. For the analysis of 3,3',4,4'-tetrachlorobiphenyl (TCB), 3,4,4',5-TCB, 3,3',4,4',5-pentachlorobiphenyl (PeCB), and 3,3',4,4',5,5'-hexachlorobiphenyl (HxCB), we used [$^{13}C_{12}$]-3,3',4,

4'-TCB, [$^{13}C_{12}$]-3,4,4',5-TCB, [$^{13}C_{12}$]-3,3',4,4',5-PeCB, and [$^{13}C_{12}$]-3,3',4,4',5,5'-HxCB as internal standards, respectively. [$^{13}C_{12}$]-1,2,3,4-TCDD was used as a syringe spike.

4. Data analysis

To estimate the sum of TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs, we introduced ND (less than the detection limit) values to half values of the detection limit and the estimates based on the toxic equivalency factors (TEF) values proposed by the World Health Organization (WHO)[9].

Results and discussion

The concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho patients and Yusho-suspected persons in 2004-2005, including the dates in 2002-2003 and the normal controls that had been previously reported, are presented in Table 1-4[5)~7)]. The sum of TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho patients in 2002-2005 were 136.4, 125.0, 126.1, and 124.2 pg TEQ/g

Table 1 Concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho patients collected in 2002-2005

	Concentration (pg/g lipid)									
	Yusho patients								Normal controls	
	2002 (n=279)		2003 (n=269)		2004 (n=242)		2005 (n=237)		2005 (n=127)	
Congeners	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
2,3,7,8-TCDD	1.7	0.8	1.7	0.8	1.4	0.8	1.6	1.4	1.9	0.8
1,2,3,7,8-PeCDD	11.1	5.9	9.7	5.4	9.7	5.6	10.4	6.0	9.0	3.4
1,2,3,4,7,8-HxCDD	2.9	1.8	2.6	1.6	2.6	1.6	3.0	1.9	3.6	1.9
1,2,3,6,7,8-HxCDD	53.0	41.7	50.4	42.6	49.2	41.5	50.8	40.8	27.7	11.0
1,2,3,7,8,9-HxCDD	5.1	3.8	3.9	2.7	4.3	3.1	4.8	3.2	4.5	2.8
1,2,3,4,6,7,8-HpCDD	63.4	53.7	38.6	22.9	49.8	25.9	46.8	30.2	78.7	55.5
OCDD	877.2	728.2	763.3	438.9	716.8	370.3	797.4	636.9	1221.6	940.4
2,3,7,8-TCDF	1.4	0.9	1.2	0.7	1.8	1.6	3.0	3.8	1.0	0.7
1,2,3,7,8-PeCDF	0.9	0.8	0.8	0.7	0.9	0.8	1.3	1.7	0.7	0.6
2,3,4,7,8-PeCDF	192.0	252.1	176.2	240.2	181.8	241.7	175.1	240.1	17.1	6.6
1,2,3,4,7,8-HxCDF	59.0	99.6	52.0	87.2	50.4	83.8	48.1	86.2	4.9	2.7
1,2,3,6,7,8-HxCDF	22.4	29.1	20.4	27.0	18.6	24.5	18.3	26.1	5.7	2.6
2,3,4,6,7,8-HxCDF	ND		ND		ND		ND		ND	
1,2,3,7,8,9-HxCDF	ND		ND		ND		ND		ND	
1,2,3,4,6,7,8-HpCDF	3.2	4.0	2.8	2.6	2.7	3.1	2.7	2.7	2.2	2.1
1,2,3,4,7,8,9-HpCDF	ND		ND		ND		ND		ND	
OCDF	ND		ND		ND		ND		ND	
3,4,4',5-TCB (# 81)	5.6	3.1	5.3	1.8	5.5	3.0	5.5	2.3	5.6	2.3
3,3',4,4'-TCB (# 77)	11.0	7.2	8.6	6.4	11.0	8.2	11.0	20.5	8.4	4.8
3,3',4,4',5-PeCB (# 126)	103.1	71.7	98.1	65.3	92.3	70.4	94.6	64.4	113.1	80.6
3,3',4,4',5,5'-HxCB (# 169)	200.0	154.5	183.8	139.2	135.4	98.5	155.4	113.2	63.7	27.0
Total PCDDs	1014.3	782.0	870.3	469.5	833.8	407.5	914.8	673.1	1346.9	1005.7
Total PCDFs	284.3	374.6	258.8	352.3	261.8	347.9	253.7	353.7	36.9	13.5
Total PCDDs / PCDFs	1298.7	866.0	1129.1	602.3	1095.6	561.5	1168.4	769.8	1383.9	1012.2
Total non-*ortho* PCBs	319.9	186.5	295.9	167.6	244.3	138.2	266.6	147.6	190.7	106.3
Total	1618.6	947.8	1425.0	703.4	1339.9	644.9	1435.0	837.1	1574.6	1047.6
PCDDs-TEQ	19.5	10.4	17.6	9.9	17.3	10.1	18.4	10.7	15.3	5.8
PCDFs-TEQ	104.6	137.9	95.8	131.1	98.3	131.3	94.8	131.2	10.0	3.8
PCDDs/PCDFs-TEQ	124.1	146.7	113.3	139.7	115.5	139.8	113.2	140.2	25.4	9.0
Non-*ortho* PCBs-TEQ	12.3	7.7	11.7	6.9	10.6	7.3	11.0	6.8	11.9	8.2
Total of TEQ	136.4	148.3	125.0	141.2	126.1	140.7	124.2	141.5	37.3	15.9
Lipid (%)	0.34	0.06	0.36	0.06	0.35	0.05	0.34	0.05	0.33	0.05
Age (years)	63.6	12.6	65.7	11.7	65.5	11.8	67.3	11.3	68.0	5.4

The participants of the medical check-up for Yusho during 2002 to 2005 were 371, 343, 316, and 351, for each year respectively

ND : less than the detection limit : S.D. : standard deviation : TEQ : toxic equivalents.

Table 2 Concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho-suspected persons collected in 2002-2005

	Concentration (pg/g lipid)									
	Yusho-suspected persons								Normal controls	
	2002 (n=92)		2003 (n=74)		2004 (n=74)		2005 (n=114)		2005 (n=127)	
Congeners	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
2,3,7,8-TCDD	1.4	0.9	1.5	0.7	1.5	0.9	1.6	1.1	1.9	0.8
1,2,3,7,8-PeCDD	7.8	4.0	6.6	3.2	6.8	3.3	7.9	4.1	9.0	3.4
1,2,3,4,7,8-HxCDD	3.1	1.9	2.4	1.4	2.8	1.5	3.2	1.9	3.6	1.9
1,2,3,6,7,8-HxCDD	28.7	18.8	26.0	17.1	25.7	13.0	26.5	14.4	27.7	11.0
1,2,3,7,8,9-HxCDD	5.4	3.9	3.6	2.1	4.2	2.0	4.8	2.7	4.5	2.8
1,2,3,4,6,7,8-HpCDD	76.4	55.1	39.8	24.1	59.0	35.6	51.2	29.3	78.7	55.5
OCDD	908.9	560.1	796.2	589.2	849.9	535.8	856.4	568.3	1221.6	940.4
2,3,7,8-TCDF	1.0	0.8	1.0	0.6	1.0	0.6	1.8	2.8	1.0	0.7
1,2,3,7,8-PeCDF	0.8	0.6	0.7	0.6	0.7	0.4	1.1	1.3	0.7	0.6
2,3,4,7,8-PeCDF	33.2	51.9	30.0	50.3	15.1	15.6	24.7	36.4	17.1	6.6
1,2,3,4,7,8-HxCDF	9.2	15.5	8.3	14.6	4.4	3.4	6.0	7.2	4.9	2.7
1,2,3,6,7,8-HxCDF	6.9	5.2	6.3	5.7	4.8	2.5	5.4	3.7	5.7	2.6
2,3,4,6,7,8-HxCDF	ND		ND		ND		ND		ND	
1,2,3,7,8,9-HxCDF	ND		ND		ND		ND		ND	
1,2,3,4,6,7,8-HpCDF	3.3	4.0	3.6	3.9	2.6	2.1	2.5	2.1	2.2	2.1
1,2,3,4,7,8,9-HpCDF	ND		ND		ND		ND		ND	
OCDF	ND		ND		ND		ND		ND	
3,4,4',5-TCB (# 81)	5.4	1.6	5.2	0.9	5.1	0.8	5.9	4.1	5.6	2.3
3,3',4,4'-TCB (# 77)	10.6	6.7	7.8	4.2	11.3	7.2	15.1	27.6	8.4	4.8
3,3',4,4',5-PeCB (# 126)	91.6	78.0	75.9	61.4	78.2	65.3	98.2	91.5	113.1	80.6
3,3',4,4',5,5'-HxCB (# 169)	83.1	68.2	74.0	58.7	49.7	34.3	70.2	82.3	63.7	27.0
Total PCDDs	1031.7	617.7	876.0	620.9	949.8	580.8	951.6	609.8	1346.9	1005.7
Total PCDFs	59.9	72.2	55.3	69.1	34.0	21.4	46.6	47.3	36.9	13.5
Total PCDDs / PCDFs	1091.6	643.9	931.3	652.8	983.8	588.7	998.2	625.2	1383.9	1012.2
Total non-*ortho* PCBs	190.8	136.8	162.9	113.6	144.4	96.9	189.3	156.0	190.7	106.3
Total	1282.4	732.4	1094.2	719.9	1128.2	646.2	1187.6	707.4	1574.6	1047.6
PCDDs-TEQ	13.8	6.9	11.7	5.4	12.2	5.6	13.6	6.8	15.3	5.8
PCDFs-TEQ	18.7	27.8	16.9	26.9	8.9	8.3	14.0	19.2	10.0	3.8
PCDDs/PCDFs-TEQ	32.5	31.3	28.6	30.2	21.1	12.0	27.5	23.5	25.4	9.0
Non-*ortho* PCBs-TEQ	10.0	41.9	8.3	6.6	8.3	6.8	10.5	9.5	11.9	8.2
Total TEQ	42.5	35.2	37.0	32.9	29.4	16.9	38.1	29.8	37.3	15.9
Lipid (%)	0.33	0.07	0.35	0.05	0.33	0.06	0.33	0.05	0.33	0.05
Age (years)	54.1	17.4	51.8	20.3	54.7	17.0	54.7	17.0	68.0	5.4

The participants of the medical check-up for Yusho during 2002 to 2005 were 371, 343, 316, and 351, for each year respectively

ND : less than the detection limit : S.D. : standard deviation : TEQ : toxic equivalents.

lipid for each year, respectively, and the concentrations were 3.7, 3.4, 3.4, and 3.3 times higher than those in the normal controls for each year, respectively (Table 1). In the case of Yusho-suspected persons, the concentrations were 42.5, 37.0, 29.4, and 38.1 pg TEQ/g lipid, respectively, which were slightly higher than those of the normal controls (Table 2).

The TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho patients were 19.5, 104.6, and 12.3 pg TEQ/g lipid in 2002, respectively, 17.6, 95.8, and 11.7 pg TEQ/g lipid in 2003, respectively, 17.3, 98.3, and 10.6 pg TEQ/g lipid in 2004, respectively, and 18.4, 94.8, and 11.0 pg TEQ/g lipid in 2005, respectively (Table 1). In the case of Yusho-suspected persons, these concentrations were 13.8. 18.7, and 10.0 pg TEQ/g lipid in 2002, respectively, 11.7, 16.9, and 8.3 pg TEQ/g lipid in 2003, respectively, 12.2, 8.9, and 8.3 pg TEQ / g lipid in 2004, respectively, and 13.6, 14.0, and 10.5 pg TEQ / g lipid in 2005,

Table 3 Concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho patients collected in 2002-2005

	Concentration				
	Yusho patients				Normal controls
	2002 (n=279)	2003 (n=269)	2004 (n=242)	2005 (n=237)	2005 (n=127)
Total of TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs (pg TEQ/g lipid)					
Maximum	1126.1	1176.6	980.3	1005.0	99.7
Minimum	7.0	5.5	5.6	8.7	12.3
Mean	136.4	125.0	126.1	124.2	37.3
S.D.	148.3	141.2	140.7	141.5	15.9
Concentration of PCDFs (pg TEQ/g lipid)					
Maximum	1029.4	1074.4	897.4	910.4	21.6
Minimum	2.1	1.8	2.0	2.1	3.5
Mean	104.6	95.8	98.3	94.8	10.0
S.D.	137.9	131.1	131.3	131.2	3.8
Concentration of 2,3,4,7,8-PeCDF (pg /g lipid)					
Maximum	1889.7	1953.5	1641.5	1672.6	36.8
Minimum	3.1	2.6	2.9	3.2	6.0
Mean	192.0	176.2	181.8	175.1	17.1
S.D.	252.1	240.2	241.7	240.1	6.6

The participants of the medical check-up for Yusho during 2002 to 2005 were 371, 343, 316, and 351, for each year respectively

ND : less than the detection limit : S.D. : standard deviation : TEQ : toxic equivalents.

Table 4 Concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of Yusho-suspected persons collected in 2002-2005

	Concentration				
	Yusho-suspected persons				Normal controls
	2002 (n=92)	2003 (n=74)	2004 (n=74)	2005 (n=114)	2005 (n=127)
Total of TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs (pg TEQ/g lipid)					
Maximum	178.0	188.5	93.5	175.7	99.7
Minimum	6.7	3.9	3.8	7.4	12.3
Mean	42.5	37.0	29.4	38.1	37.3
S.D.	35.2	32.9	16.9	29.8	15.9
Concentration of PCDFs (pg TEQ/g lipid)					
Maximum	145.2	150.9	69.9	136.2	21.6
Minimum	1.6	1.1	1.4	1.6	3.5
Mean	18.7	16.9	8.9	14.0	10.0
S.D.	27.8	26.9	8.3	19.2	3.8
Concentration of 2,3,4,7,8-PeCDF (pg /g lipid)					
Maximum	262.7	272.4	131.9	259.5	36.8
Minimum	2.2	1.2	1.9	2.2	6.0
Mean	33.2	30.0	15.1	24.7	17.1
S.D.	51.9	50.3	15.6	36.4	6.6

The participants of the medical check-up for Yusho during 2002 to 2005 were 371, 343, 316, and 351, for each year respectively

ND : less than the detection limit : S.D. : standard deviation : TEQ : toxic equivalents.

Table 5 Relative concentration ratios of the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs to the total concentrations

	Relative contribution ratio (%)								
	Yusho patients				Yusho-suspected persons				Normal controls
Isomers	2002	2003	2004	2005	2002	2003	2004	2005	2005
PCDDs	14.3	14.1	13.7	14.8	32.6	31.8	41.5	35.6	41.1
PCDFs	76.7	76.6	77.9	76.3	43.9	45.7	30.2	36.7	26.8
Non-*ortho* PCBs	9.0	9.3	8.4	8.9	23.5	22.5	28.3	27.6	32.0

respectively (Table 2). On the other hand, the TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of normal controls were 15.3, 10.0, and 11.9 pg TEQ / g lipid, respectively. The TEQ concentrations of PCDDs and non-*ortho* PCBs were nearly the same among Yusho patients, Yusho-suspected persons, and normal controls in 2002-2005. However, the PCDF levels of Yusho patients were significantly higher than those of Yusho-suspected persons and normal controls. The PCDFs concentrations of the Yusho patients in 2002-2005 were 10.5, 9.6, 9.8, and 9.5 times higher than those of normal controls for each year, respectively (Table 1), and those of the Yusho-suspected persons were about 1.9, 1.7, 0.9, and 1.4 times higher than those of normal controls for each year, respectively (Table 2).

The relative contribution ratios of the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs to the total concentrations are shown in Table 5. The ratios of the PCDDs, PCDFs, and non-*ortho* PCBs concentrations to the total concentrations of these dioxin-like compounds for normal controls were 41.1, 26.8, and 32.0%, respectively. In the case of Yusho-suspected persons, the contribution ratios of these three concentrations were 32.6, 43.9, and 23.5% in 2002, respectively, 31.8, 45.7, and 22.5%

Table 6 Concentrations of each congener for 138 Yusho patients in whom the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs were measured every year during 2002 to 2005

	Concentration (pg/g lipid)							
	2002		2003		2004		2005	
Congeners	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
2,3,7,8-TCDD	1.6	0.8	1.6	0.8	1.3	0.7	1.6	1.6
1,2,3,7,8-PeCDD	11.2	6.3	9.7	5.6	9.7	5.4	10.6	6.3
1,2,3,4,7,8-HxCDD	3.1	1.8	2.6	1.5	2.7	1.6	3.0	1.8
1,2,3,6,7,8-HxCDD	55.5	44.1	52.4	46.5	50.7	41.0	52.8	41.5
1,2,3,7,8,9-HxCDD	5.4	3.3	4.0	2.8	4.3	3.0	4.6	3.1
1,2,3,4,6,7,8-HpCDD	71.5	61.7	38.8	22.6	51.5	27.2	46.5	26.9
OCDD	949.9	871.7	769.8	407.9	745.1	388.7	772.3	434.4
2,3,7,8-TCDF	1.4	1.0	1.3	0.7	1.5	1.1	3.0	3.9
1,2,3,7,8-PeCDF	1.0	0.9	0.9	0.7	0.8	0.7	1.2	1.7
2,3,4,7,8-PeCDF	205.1	280.4	184.0	262.9	178.9	245.6	180.6	251.1
1,2,3,4,7,8-HxCDF	59.9	102.7	55.4	100.5	49.1	85.9	49.5	87.1
1,2,3,6,7,8-HxCDF	22.3	29.6	21.2	31.0	18.1	23.9	18.7	25.1
2,3,4,6,7,8-HxCDF	ND		ND		ND		ND	
1,2,3,7,8,9-HxCDF	ND		ND		ND		ND	
1,2,3,4,6,7,8-HpCDF	3.2	3.8	3.0	2.7	2.8	2.7	2.8	2.5
1,2,3,4,7,8,9-HpCDF	ND		ND		ND		ND	
OCDF	ND		ND		ND		ND	
3,4,4',5-TCB (# 81)	5.6	3.0	5.4	1.8	5.4	2.3	5.4	2.3
3,3',4,4'-TCB (# 77)	11.7	7.7	8.1	5.1	10.6	8.5	8.8	13.8
3,3',4,4',5-PeCB (# 126)	103.3	71.1	91.7	57.5	88.7	60.1	93.8	60.8
3,3',4,4',5,5'-HxCB (# 169)	205.5	162.2	185.0	148.5	141.6	104.1	157.9	118.9
Total PCDDs	1098.3	930.7	878.8	433.2	865.3	423.2	891.5	465.7
Total PCDFs	298.5	410.3	271.2	392.9	256.6	353.4	261.0	365.6
Total PCDDs/PCDFs	1396.8	1003.7	1150.0	585.2	1121.9	555.4	1152.4	594.3
Total non-*ortho* PCBs	326.2	188.8	290.2	170.0	246.4	133.0	265.9	148.5
Total	1723.0	1079.7	1440.2	694.2	1368.3	634.7	1418.3	678.6
PCDDs-TEQ	20.1	11.0	17.7	10.4	17.4	9.7	18.8	10.9
PCDFs-TEQ	111.3	153.0	100.1	144.3	96.6	133.4	97.7	136.8
PCDDs/PCDFs-TEQ	131.4	162.5	117.8	153.5	114.0	141.7	116.5	145.9
Non-*ortho* PCBs-TEQ	12.4	7.5	11.0	6.2	10.3	6.3	11.0	6.5
Total of TEQ	143.7	163.8	128.9	154.9	124.3	142.4	127.5	147.1

ND : less than the detection limit : S.D. : standard deviation : TEQ : toxic equivalents.

in 2003, respectively, 41.5, 30.2, and 28.3% in 2004, respectively, and 35.6, 36.7, and 27.6% in 2005, respectively. Interestingly, the ratios of these concentrations in Yusho patients were 14.3, 76.7, and 9.0% in 2002, respectively, 14.1, 76.6, and 9.3% in 2003, respectively, 13.7, 77.9, and 8.4% in 2004, respectively, and 14.8, 76.3, and 8.9% in 2005, respectively. Yusho patients had the highest contribution ratio of PCDFs to total of TEQ concentration of these dioxin-like compounds. When the PCDFs ratio to the total of TEQ concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in Yusho-suspected persons was compared with that of Yusho patients and normal controls, it was at an intermediate level between that of Yusho patients and normal controls. However, the maximum concentrations of PCDFs in the Yusho-suspected persons group during 2002 to 2005 were 145.2, 150.9, 69.9, and 136.2 pg TEQ / g lipid for each year, respectively (Table 4). These finding indicated that some of the Yusho-suspected persons have a high PCDFs concentrations in their blood.

Among PCDFs congeners, the concentration of 2,3,4,7,8-PeCDF showed particularly high concentration for Yusho patients compared with that of normal controls (Table 1). The concentrations of 2,3,4,7,8-PeCDF in the blood samples collected in 2002-2005 for Yusho patients were 192.0, 176.2, 181.8, and 175.1 pg / g lipid for each year, respectively. These levels were 11.2, 10.3, 10.6, and 10.2 times higher than those of normal controls for each year, respectively (Table 1). The maximum concentrations of 2,3,4,7,8-PeCDF in the Yusho patients group during 2002 to 2005 were 1889.7, 1953.5, 1641.5, and 1672.6 pg / g lipid for each year, respectively (Table 3). It is surprising that 2,3,4,7,8-PeCDF in one patient with severe Yusho symptoms remains at a much higher concentration than normal controls even now. In the case of Yusho-suspected persons, the concentrations were 1.9, 1.8, 0.9, and 1.4 times higher than those of normal controls for each year during 2002 to 2005, respectively (Table 2). However, the maximum concentrations of 2,3,4,7,8-PeCDF in the Yusho-suspected persons group during 2002 to 2005 were 262.7, 272.4, 131.9, and 259.5 pg / g lipid for each year, respectively, which suggested that some of the Yusho-suspected persons were in fact exposed to PCDFs (Table 4). From the results measured in this study, we reconfirmed that Yusho patients still have a much higher concentration of PCDFs in their blood than do unaffected persons and that some of the Yusho-suspected persons showed high PCDFs concentrations in their blood. We also reconfirmed that the concentration of 2,3,4,7,8-PeCDF, which was the highest among the congeners of PCDFs, was about 10 times higher than that of the normal controls.

Among 279, 269, 242, and 237 Yusho patients who received medical check-up between 2002 and 2005, the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in the blood of 138 patients were measured for 4 consecutive years. The average PCDFs concentrations for the 138 Yusho patients in 2002-2005 were 111.3, 100.1, 96.6, and 97.7 pg TEQ / g lipid, respectively, and the concentrations did not significantly decrease during 2002 to 2005 (Table 6). The concentrations of 2,3,4,7,8- PeCDF among PCDFs congeners were 205.1, 184.0, 178.9, and 180.6 pg / g lipid in 2002-2005 for each year, respectively, and the concentrations remained unchanged from year to year (Table 6). These findings suggest that the PCDFs remained in the blood of Yusho

patients for a very long time, 37 years having passed since the outbreak of Yusho, have a very high persistency.

We measured the concentrations of PCDDs, PCDFs, and non-*ortho* PCBs in blood collected from 279, 269, 242, and 237 Yusho patients during medical check-up performed in 2002 to 2005, respectively, and 92, 74, 74, and 114 Yusho-suspected persons during those same years, respectively. Based on the results of this follow- up survey study, the concentration of 2,3,4,7,8 -PeCDF in the blood officially became part of the diagnostic criteria for Yusho exposure on September 29, 2004. As a result, of 74, 74, and 114 Yusho-suspected persons measured during 2003 to 2005, respectively, 18, 7, and 14 persons were officially registered as Yusho patients based on the "New Diagnostic Criteria," respectively. Because Yusho patients and Yusho-suspected persons have become older, it has become difficult to distinguish their age-related senile clinical symptoms from symptoms peculiar to Yusho disease. By continuing this follow-up survey in the future, some of Yusho-suspected persons will finally be registered as Yusho patients based on the new diagnostic criteria.

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平成 16 および 17 年度の油症検診における血液中ダイオキシン類濃度

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平成 16 年度に日本在住の 242 名の油症患者と 74 名の未認定者および平成 17 年度に日本在住の 237 名の油症患者と 114 名の未認定者から採取した血液中の PCDDs, PCDFs, および non-*ortho* PCBs 濃度を測定し, 平成 15 年度に測定した一般健常人の結果と比較した. 平成 16 および 17 年度に受診した油症患者の血液中 PCDDs, PCDFs, および non-*ortho* PCBs の総 toxic equivalents (TEQ) 濃度は, それぞれ 126.1 および 124.2 pg TEQ / g lipid で, その濃度は一般健常人のそれぞれ 3.4 倍および 3.3 倍であった. 未認定者の場合, 総 TEQ 濃度は, それぞれ一般健常人の 0.8 倍および 1.0 倍であった. 油症患者の血液中 PCDDs および non-*ortho* PCBs 濃度は, ほぼ健常人と同レベルなのに対し, PCDFs 濃度は一般健常人のそれぞれ 9.8 倍 (平成 16 年) および 9.5 倍 (平成 17 年) 高い値を示した. 油症患者の血液中 PCDFs 異性体間で特に高濃度を示す 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PeCDF) は, 健常人のそれぞれ 10.6 倍 (平成 16 年) および 10.2 倍 (平成 17 年) 高い値を示した. 未認定者の 2,3,4,7,8-PeCDF 濃度は, 健常人のそれぞれ 0.9 倍および 1.4 倍であった. しかしながら, 未認定者の中には一般健常人と比較して異常に高い 2,3,4,7,8-PenCD 濃度を示す人が数名認められた. これまでに行った追跡調査の結果を基に, 2,3,4,7,8-PenCDF 濃度を追補した新しい診断基準が平成 16 年 9 月 29 日に策定され, 平成 16 年度に受診した 74 名の未認定者のうち 7 名が, 平成 17 年度も 114 名の未認定者のうち 14 名が新たに油症認定者と診定された.