SEX DIFFERENCE AS IT IS RELATED TO THE DIOXIN CONCENTRATIONS IN THE BLOOD OF YUSHO PATIENTS

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Introduction

In 1968, a case of mass poisoning, the so-called Yusho incident[1], occurred in western Japan due to the contamination of cooking oil by heat-degraded polychlorinated biphenyls (PCBs). Based on the results of a survey, the cause of Yusho disease is thought to be ingested toxic substances, including not only PCBs but also polychlorinated dibenzofuran (PCDFs), polychlorinated quarterphenyls (PCQs), and polychlorinated terphenyls (PCTs) in Kanemi rice oil. The medical aspects of this poisoning have been demonstrated by many researchers. Since 1995, extensive studies have been performed by the Yusho study group involving follow-up surveys of the human tissues and/or blood concentrations of the causal compounds in Yusho patients as well as clinical trials to examine the acceleration of the excretion of these compounds in Yusho patients.

We have reported that high levels of toxic substances such as PCDFs (2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, and 1,2,3,6,7,8-HxCDF) have persisted in Yusho patients even up through 1995, more than 27 years after the original incident[2]. The data obtained in the latest follow-up survey was reported in Dioxin 2006-2007[3,4]. We have measured dioxin concentrations in the blood of 649 Yusho patients in annual medical examinations from 2001 to 2009. We determined that the concentrations of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 3,3',4,4',5,5'-HxCB(#169) in the blood of Yusho patients were more than twice as high levels as those of normal controls.

In the present study, we compared the concentrations of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 3,3',4,4',5,5'-HxCB(#169) in the blood of male Yusho patients with those of female Yusho patients. We found that the mean concentrations of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 3,3',4,4',5,5'-HxCB(#169) in female Yusho patients were 2.9, 3.7, 2.4, and 1.3 times higher, respectively, than those of male Yusho patients.

Materials and Methods

A total of 1,678 blood samples were collected from 649 Yusho patients (male: 312, female: 337) who had given their informed consent at their medical checkups through the fiscal years 2001 to 2009. We analyzed the latest dioxin concentrations in the blood samples of these patients. Blood samples from a total of 127 normal controls were also collected in Fukuoka prefecture in 2004. The ages of the controls ranged from 60 to 86 years old, which matches the age of the Yusho patients. Ten-milliliter blood samples were collected using a vacuum

blood collecting pipe containing heparin and stored at 4°C for later analysis. The details of the method of blood lipid extraction, purification, and mass-spectrometric measurement have been described elsewhere[5,6]. To estimate the toxic equivalent quantities (TEQs) and total concentrations of PCBs, we introduced ND (less than the detection limit) values to half values of the detection limit.

Table 1 PCDD, PCDF and non-ortho PCB concentrations in the blood of Yusho patients and normal controls.

	Yusho Patients (2001-2009)				Normal controls (2004)			
Congeners	Mean	SD	Min	Max	Mean	SD	Min	Max
2,3,7,8-TCDD	1.6	1.0	ND	8.6	1.9	0.8	ND	4.3
1,2,3,7,8-PeCDD	9.8	5.7	ND	43	9.0	3.4	3.2	20
1,2,3,4,7,8-HxCDD	2.9	1.9	ND	15	3.6	1.9	ND	13
1,2,3,6,7,8-HxCDD	44	37.6	3.9	310	28	11.0	7.3	70
1,2,3,7,8,9-HxCDD	4.7	3.4	ND	31	4.5	2.8	ND	16
1,2,3,4,6,7,8-HpCDD	51	32.8	ND	320	78	55.4	18	470
OCDD	760	534.3	150	7900	1200	938.3	181	7600
Total PCDD	880	577.6	180	8300	1200	1003.4	214	8100
2,3,7,8-TCDF	2.0	2.7	ND	48	1.0	0.7	ND	4.5
1,2,3,7,8-PeCDF	1.1	1.6	ND	27	0.7	0.5	ND	4.6
2,3,4,7,8-PeCDF	140	203.4	2.9	1800	17	6.6	6.0	37
1,2,3,4,7,8-HxCDF	37	69.9	ND	580	5.0	2.7	ND	20
1,2,3,6,7,8-HxCDF	15	20.9	ND	180	5.7	2.6	ND	16
2,3,4,6,7,8-HxCDF	1.2	0.8	ND	9.8	1.2	0.8	ND	5.2
1,2,3,7,8,9-HxCDF	ND				ND			
1,2,3,4,6,7,8-HpCDF	3.1	11.2	ND	280	2.2	2.1	ND	14
1,2,3,4,7,8,9-HpCDF	1.0	0.1	ND	3.7	ND			
OCDF	2.3	5.5	ND	140	2.1	1.4	ND	18
Total PCDF	200	292.5	12	2600	37	13.5	15	86
3,4,4',5-TCB(#81)	5.6	3.0	ND	37	5.6	2.3	ND	24
3,3',4,4'-TCB(#77)	8.4	14.9	ND	290	8.4	4.8	ND	31
3,3',4,4',5-PeCB(#126)	93	75.9	ND	590	110	80.5	17	520
3,3',4,4',5,5'-HxCB(#169)	160	124.3	10	1100	64	27.0	16	190
Total Non-ortho PCBs	270	171.0	27	1200	190	105.9	59	740
Total	1300	774.5	310	8600	1500	1047.6	290	8400
◆【WHO-05】◆								
T PCDDs-06-TEQ	17	10.2	2.8	80	16	5.9	5.1	35
T PCDFs-06-TEQ	47	69.7	1.4	610	6.6	2.5	2.3	14
T Non-ortho PCBs-06-TEQ	14	9.6	0.9	67	13	8.6	2.6	58
Total 06-TEQ	78	82.0	5.5	730	35	15.3	11	98
Lipid(%)	0.3	0.1	0.2	0.6	0.3	0.1	0.2	0.5
Age(years)	67.0	14.2	32	98	68.0	5.4	60	86

(pg/g lipid)

CB: chlorinated biphenyl; CDD: chlorinated dibenzo-p-dioxins; CDF: chlorinated dibenzofurans; Hx: hexa; Hp: hepta; ND: less than the determination limit; OCDD: octachlorodibenzo-p-dioxin; OCDF: octachlorodibenzofurans; PCB: polychlorinated biphenyl; PCDD:polychlorinated dibenzo-p-dioxin;PCDF:polychlorinated dibenzofuran; Pe:penta; TCB:tetrachlorobipheny; TCDD:tetrachlorodibenzo-p-dioxin; TCDF:tetrachlorodivenzofuran; TEQ:toxic equivalent quantity.

Results and Discussion

Table 1 shows the concentrations of PCDD, PCDF, and non-orth PCB congeners in the blood of Yusho patients and of normal controls. In 649 Yusho patients, the mean total TEQ concentration in the blood was 78 pg-TEQ/g lipid. However, the mean level found in the normal controls was 38 pg-TEQ/g lipid. The level of total TEQ in the Yusho patients was 2.1 times higher than that of the normal controls. The mean concentrations of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 3,3',4,4',5,5'-HxCB(#169) in the blood of

Yusho patients were 140, 37, 15, and 160 pg/g lipid, respectively, while the levels found in the normal controls were 17, 5.0, 5.7, and 64 pg/g lipid, respectively. The levels of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 3,3',4,4',5,5'-HxCB(#169) were 8.2, 7.4, 2.6, and 2.5 times higher than those of normal controls, respectively, and even after the passage of 36-38 years, the levels of these four substances remain high in victims of this incident.

Table 2 PCDD, PCDF and non-ortho PCB concentrations in the blood of Yusho patients, male and female

	Yusho Patients (2001-2009)							
	Male (N=312)				Female (N=337)			
Congeners	Mean	SD	Min	Max	Mean	SD	Min	Max
2,3,7,8-TCDD	1.4	0.8	ND	4.4	1.8	1.1	ND	8.6
1,2,3,7,8-PeCDD	8.0	4.0	ND	22	12	6.5	1.2	43
1,2,3,4,7,8-HxCDD	2.6	1.7	ND	12	3.2	2.0	ND	15
1,2,3,6,7,8-HxCDD	33	23.9	3.9	150	54	44.3	6.5	310
1,2,3,7,8,9-HxCDD	4.0	2.7	ND	24	5.3	3.8	ND	31
1,2,3,4,6,7,8-HpCDD	49	32.9	ND	290	52	32.7	ND	320
OCDD	710	424.9	150	3900	810	615.2	180	7900
Total PCDD	810	466.9	180	4300	940	658.3	240	8300
2,3,7,8-TCDF	1.7	3.2	ND	48	2.3	2.2	ND	14
1,2,3,7,8-PeCDF	1.1	1.9	ND	27	1.2	1.2	ND	7.6
2,3,4,7,8-PeCDF	68	93.7	3.0	560	200	251.0	2.9	1800
1,2,3,4,7,8-HxCDF	15	25.4	ND	200	57	89.4	ND	580
1,2,3,6,7,8-HxCDF	8.9	9.5	ND	77	21	26.3	ND	180
2,3,4,6,7,8-HxCDF	1.2	0.7	ND	8.0	1.2	0.9	ND	9.8
1,2,3,7,8,9-HxCDF	ND				ND			
1,2,3,4,6,7,8-HpCDF	2.4	2.7	ND	26	3.8	15.4	ND	280
1,2,3,4,7,8,9-HpCDF	ND				1.0	0.2	ND	3.7
OCDF	ND				2.5	7.6	ND	140
Total PCDF	100	127.1	12	800	300.0	364.0	13	2600
3,4,4',5-TCB(#81)	5.8	3.9	ND	37	5.3	1.8	ND	24
3,3',4,4'-TCB(#77)	9.0	18.6	ND	290	7.8	10.4	ND	150
3,3',4,4',5-PeCB(#126)	95	88.7	ND	590	90	61.7	ND	430
3,3',4,4',5,5'-HxCB(#169)	140	100.8	10.4	640	180	140.7	12	1100
Total Non-ortho PCBs	250	175.7	27.2	1100	280	165.5	36	1200
◆【WHO-05】◆								
T PCDDs-05-TEQ	14	6.9	2.8	38	20	11.7	3.1	80
T PCDFs-05-TEQ	23	31.3	1.4	190	69	86.3	1.4	610
T Non-ortho PCBs-05-TEQ	14	10.9	0.9	67	14	8.1	1.8	46
Total -TEQ(WHO-05)	51	41.4	5.5	240	100	100.1	6.2	730
Lipid(%)	0.33	0.05	0.20	0.53	0.34	0.05	0.23	0.64
Age(years)	65.9	14.7	32	95	67.9	13.6	37	98

(pg/g lipid)

CB: chlorinated biphenyl; CDD: chlorinated dibenzo-p-dioxins; CDF: chlorinated dibenzofurans; Hx: hexa; Hp: hepta; ND: less than the determination limit; OCDD: octachlorodibenzo-p-dioxin; OCDF: octachlorodibenzofurans; PCB: polychlorinated biphenyl; PCDD:polychlorinated dibenzo-p-dioxin; PCDF:polychlorinated dibenzofuran; Pe:penta; TCB:tetrachlorobipheny; TCDD:tetrachlorodibenzo-p-dioxin; TCDF:tetrachlorodivenzofuran;TEQ:toxic equivalent quantity.

Table 2 shows the concentrations of PCDD, PCDF, and non-ortho PCB congeners in the blood of male and female Yusho patients. The mean total TEQ concentrations in the blood of male Yusho patients was 51 pg-TEQ/g lipid, while that in the female Yusho patients was 100 pg-TEQ/g lipid. The level of total TEQ in the female Yusho patients was 2 times higher than that of male Yusho patients. The mean concentrations of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, and 3,3',4,4',5,5'-HxCB(#169) in the blood of male

Yusho patients were 68, 15, 8.9, and 140 pg /g lipid, respectively, and the mean concentrations found in the female Yusho patients were 200, 57, 21, and 180 pg/g lipid, respectively, which are 2.9, 3.8, 2.4, and 1.3 times higher than those of male Yusho patients, respectively. These sex differences in the dioxin concentration levels in the blood were not found in the normal controls. These results indicated that dioxin and organohalogen compounds were usually saved in fat tissue, and women saved more body fat in comparison with men.

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