FOLLOW-UP SURVEY OF DIOXINS CONCENTRATIONS IN THE BLOOD OF YUSHO PATIENTS IN 2002—2005

Todaka T[1], Hirakawa H[2], Kajiwara J[2], Hori T[2], Tobiishi K[2], Iida T[2]* , Yoshimura T[2] and Furue M[1]

[1]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University , Fukuoka 812-8582, Japan,
[2]Fukuoka Institute of Health and Environmental Sciences, 39 Mukaizano, Dazaifu, Fukuoka 818-0135, Japan
*Kitakyuushu Life Science Center, 1-4 Nakabarushinmati, Tobata-ku, Kitakyushu-city, 804-0003, Japan

Introduction

In 1968, over 1800 persons in western Japan developed a strange skin disease, later named Yusho disease, which was found to have been caused by the ingestion of rice bran oil contaminated with polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), polychlorinated quarterphenyls (PCQs) and polychlorinated terphenyls (PCTs). Over 37 years have passed since this 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 research by the Yusho study group investigating this disease, PCDFs rather than PCBs have been revealed to be the primary cause of Yusho disease symptoms. However, the concentrations of PCDFs in the blood have not been included in the diagnostic criteria because the amount of blood that can be collected from Yusho patients is restricted, and thus there are practical difficulties involved in measuring these concentrations. In order to elucidate the influence of polychlorinated dibenzo-p-dioxins (PCDDs), PCDFs and non-*ortho*-coplanar PCBs (non-*ortho*-PCBs) on the health of Yusho patients, it was necessary to determine the concentrations of these compounds in the blood of Yusho patients. We therefore developed an analytic method for measuring the concentrations of PCDDs, PCDFs, and non-*ortho*-PCBs in human blood samples as small as 5 g, as well as an efficient method for speeding up the pretreatment procedure for blood samples.[1] Moreover, we improved the pretreatment procedure to allow multiple blood samples to be treated with good reproducibility in a shorter period of time.[2] Using these methods, we measured the concentrations of PCDDs, PCDFs, and non-*ortho*-PCBs in blood collected from 279, 269, 243 and 237 Yusho patients from 2002-2005, respectively, and 127 normal controls living in Fukuoka Prefecture whose ages were similar to those of the Yusho patients. We then compared the concentrations of these compounds among the groups of Yusho patients and the normal control group.

Materials and Methods

Medical health examinations for Yusho patients have been annually conducted to determine their health status. Yusho patients are officially registered based on the "Diagnostic Criteria for Yusho". In 2002-2005, blood samples were collected from Yusho patients during medical checkups; all gave their informed consent to this study. The normal controls were persons unaffected by Yusho, and selected to be in the same age range as the Yusho patients. These 127 normal controls from whom blood samples were collected also gave their informed consent. Blood samples of 10 ml were collected using a vacuum blood-collecting tube containing heparin and stored at 4°C until analyses for concentrations 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.[1,2] Concentrations of the PCDDs, PCDFs, and non-*ortho* PCBs were measured using a high resolution gas chromatography/high resolution mass spectrometry equipped with a solvent cut large volume injection system.

Results and Discussion

The total toxic equivalent quantity (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 lipid, for each year respectively, and the concentrations were 3.7, 3.4, 3.4 and 3.4 times higher than those in the normal controls for each year, respectively (Table 1). The TEQ concentrations of PCDDs and non-*ortho*-PCBs in the blood were identical in the Yusho patients and normal controls. However, the PCDFs levels of the Yusho patients were significantly higher than those of the normal controls. The PCDFs concentrations of the Yusho patients in 2002-2005 were 10.4, 9.5, 9.7 and 9.4 times higher than those of normal controls, for each year respectively. The relative

contribution ratios of PCDFs concentrations to the total TEQ concentrations for Yusho patients in 2002-2005 were 76.7, 76.6, 78.0 and 76.3%, for each year respectively; it was confirmed that the highest concentration ratio of PCDFs to the total TEQ concentrations. Of the PCDFs congeners for Yusho patients, the concentrations of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) in 2002-2005 were about 11.0, 10.1, 10.4 and 10.1 times higher than those in the normal controls for each year, respectively. Moreover, the concentration ratio of 1,2,3,4,7,8-HxCDF/1,2,3,6,7,8-HxCDF in the blood of Yusho patients exhibited a significantly higher value than that of the normal controls. Based on these results, the concentrations of 2,3,4,7,8- PeCDF in the blood officially became diagnostic criteria for Yusho on September 29th, 2004. As a result, of 117 Yusho-suspected persons who considered themselves potential victims, 18 persons were officially registered as Yusho patients based on the "New Diagnostic Criteria" in 2004.

Table 1. Concentrations of PCDDs, PCDFs, and non-*ortho* -PCBs in blood of Yusho patients and normal controls

	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	8.9	3.3
1,2,3,4,7,8-HxCDD	2.9	1.8	2.6	1.6	2.6	1.6	3.0	1.9	3.5	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	27.5	10.9
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-HeCDD	63.4	53.7	38.6	22.9	49.8	25.9	46.8	30.2	78.4	55.6
OCDD	877.2	728.2	763.3	438.9	716.8	370.3	797.4	636.9	1213.4	941.3
2,3,7,8-TCDF	1.4	0.9	1.2	0.7	1.8	1.6	3.0	3.8	0.9	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	0.5
2,3,4,7,8-PeCDF	192.0	252.1	176.2	240.2	181.8	241.7	175.1	240.1	17.4	7.6
1,2,3,4,7,8-HxCDF	59.0	99.6	52.0	87.2	50.4	83.8	48.1	86.2	5.0	2.8
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-HeCDF	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-HeCDF	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	5.5	2.2
3,3',4,4'-TCB(77)	11.0	7.2	8.6	6.4	11.0	8.2	11.0	20.5	8.3	4.7
3,3',4,4',5-PeCB(126)	103.1	71.7	98.1	65.3	92.3	70.4	94.6	64.4	109.3	72.2
3,3',4,4',5,5'-HxCB(169)	200.0	154.5	183.8	139.2	135.4	98.5	155.4	113.2	62.9	24.6
Total PCDDs	1014	782	870	470	834	407	915	673	1338	1007
Total PCDFs	284	375	259	352	262	348	254	354	37	14
Total PCDDs/PCDFs	1299	866	1129	602	1096	561	1168	770	1375	1013
Total coplanar PCBs	320	186	296	168	244	138	267	148	186	94
Total	1618	948	1425	703	1340	645	1435	837	1561	1045
PCDDs-TEQ	19.5	10.4	17.6	9.9	17.3	10.1	18.4	10.7	15.2	5.6
PCDFs-TEQ	104.6	137.9	95.8	131.1	98.3	131.3	94.8	131.2	10.1	4.3
PCDDs/PCDFs-TEQ	124.1	146.7	113.3	139.7	115.5	139.8	113.2	140.2	25.4	9.1
Coplanar PCBs-TEQ	12.3	7.7	11.7	6.9	10.6	7.3	11.0	6.8	11.6	7.4
Total TEQ	136.4	148.3	125.0	141.2	126.1	140.7	124.2	141.5	36.9	15.0
Lipid (%)	0.34	0.06	0.36	0.06	0.35	0.05	0.34	0.05	0.33	0.05

ND: less than the determination limit; S.D.: standarrd deviation; TEQ: toxic equivalent quality.

A similar poisoning caused by the ingestion of rice oil contaminated by PCBs and its thermal products occurred in Taiwan. The condition was named "Yu-Cheng" disease.[3] The symptoms were very similar to those of Yusho disease. Accidental exposure to PCDDs, PCDFs, and dioxin-like PCBs also occurred at Seveso in northern Italy, and in Russia and Austria.[4,5,6] In the Seveso, Italy and Austrian chloracne cohorts, the cause was exposure to 2,3,7,8-tetrachlorodizenzo-*p*-dioxin (TCDD). In the two cohorts in Russia, 2,3,7,8-TCDD and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (PeCDD) were the primary causal compounds. However, the principal causal compounds of Yu-Cheng and Yusho were not PCDDs but PCDF congeners: 1,2,3,4,7,8-hexachlorodibenzofuran (HxCDF) in Yu-Cheng and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) in Yusho. Therefore, intoxication from PCDFs congeners might be characteristic not only of Yusho disease, but also of Yu-Cheng disease.

Because Yusho patients still have much higher concentrations of PCDFs in their blood than unaffected people, Yusho patients remain at high risk for PCDFs toxicity. Therefore, it is necessary for this follow-up investigation to be continued so that further data that will support the health care of Yusho patients and the general population can be gathered.

Acknowledgment

This work was supported in part by a Grant-in-Aid for scientific research from the Ministry of Health Labour and Welfare, Japan.

References

1. Todaka T, Hirakawa H, Tobiihi K, Iida T. Fukuoka Igaku Zasshi 2003; 94:148.
2. Todaka T, Hirakawa H, Hori T, Tobiishi K, Iida T. J Dermatol Sci 2005; 1:21S.
3. Hsu ST, Ma CI, Hsu SK, Wu SS, Hsu NH, Yeh CC, Wu SB. Environ Health Perspect 1985; 59:5.
4. Mocarelli P, Gerthoux PM, Ferrari E, Patterson DGJr, Kieszak SM, Brambilla P, Vincoli N, Signorini S, Tramacera P, Carreri V, Sampson EJ, Turner WE, Needham LL. Lancet 2000; 355:1858.
5. Ryan JJ, Schecter A. Occup Environ Med 2000; 42:861
6. Moshammer H, Neuberger M. Lancet 2000; 356:1271.