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A Study on Polychlorinated Biphenyls Specifically -Accumulated in Blood of Yusho Patients Collected from Medical Check-Ups in 2012

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Abstract

In this study, we analyzed polychlorinated biphenyls (PCBs) in the blood of Yusho patients collected from medical check-ups, which were conducted in 2012. The results show that 65 PCB isomers, not including non-*ortho* PCBs, were detected in the blood samples, and the total concentration was 620 ng g⁻¹ lipid. This value was comparable to the concentration in blood samples collected in 2005, and indicated that PCB concentrations in Yusho patients remained unchanged from 2005 to 2012. Here, we focused on major and specific PCB isomers in the blood samples of Yusho patients and normal controls. Examples of the former include hexaCB-153, hexaCB-138, and heptaCB-180, which are detected in human blood, while the latter include hexaCB-156, hexaCB-157, and heptaCB-189, and are highly detected in the blood of Yusho patients. Additionally, we tried to determine why the specific isomers were highly accumulated in the blood of Yusho patients as compared to the normal controls. We therefore analyzed these isomers in the contaminated rice oil, and found that the concentrations of hexaCB-156, hexaCB-157, and heptaCB-189 were 1800, 450, and 190 ng g⁻¹, respectively. Notably, previous studies indicated that these isomers might not be easily metabolized in humans. Therefore, these findings demonstrated that these isomers were highly accumulated in the blood of Yusho patients.

Key words : Polychlorinated biphenyls · Blood · Rice oil · Yusho patients

Introduction

Over 40 years have passed since the Kane-mi-Yusho incident occurred in western Japan. Specifically, Yusho patients ingested rice oil products that were contaminated with large amounts of polychlorinated biphenyls (PCBs), which were used as heat-transfer medium in the process of rice oil production. Previous studies showed that the concentration of PCBs in the blood of Yusho patients decreased considerably when compared to the outbreak of Yusho

disease¹⁾⁻³⁾. However, our research group showed that some PCB isomers persisted at higher concentrations in the blood of Yusho patients after more than 40 years⁴⁾⁵⁾. Furthermore, we found two characteristic groups of PCB isomers in blood samples from affected patients. The first group of isomers consists of the major isomers (hexaCB-153, hexaCB-138, heptaCB-180, and heptaCB-182/heptaCB-187), which are generally detected in human, the other group contains specific isomers (hexaCB-156, hexaCB-157, heptaCB-181, and heptaCB-189)

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that were highly detected in the blood of Yusho patients. These isomer profiles may provide new information related to the accumulation of PCBs in human blood, as well as valuable information for metabolomics studies.

In this study, we focused on the major and specific PCB isomers in blood collected from Yusho patients during medical check-ups, which were performed in 2012. Additionally, we compared with the concentrations between this study and the results obtained from Yusho patients and the normal controls during medical check-ups in 2005. As a result, we proposed two hypotheses regarding why the specific isomers accumulated in high concentrations in the blood of Yusho patients. One possible reason was that the specific isomers were present at high concentrations in the contaminated rice oil ; alternatively, these were difficult to be metabolites such as hydroxylated polychlorinated biphenyls (OH-PCBs). Thus, we analyzed the concentrations of specific PCB isomers in the rice oil, and evaluated previous studies regarding the metabolism of PCBs in order to elucidate the differences between the concentrations of the major and specific PCB isomers in the blood of Yusho patients and that of the normal controls. Our findings could explain why the specific isomers accumulated in the blood of Yusho patients.

Materials and methods

Sampling

Medical check-ups for Yusho patients have been performed annually since the Yusho incident, in order to monitor the health status of the affected patients. The blood samples examined in this study were collected from 139 participants who received a medical check-up in 2012. Informed consent was obtained from all participants. The mean age of Yusho patients who received a medical check-up in 2012 was 62.0 years old. Additionally, the mean age of Yusho patients and normal controls who received medical check-ups in 2005 was 67.3 and 68.1

years old, respectively.

Each 10 ml of blood sample was collected using a vacuum blood-collecting tube containing heparin, and the sample was stored at 4°C until analysis. The rice oil sample was one of the products that caused the Kanemi-Yusho incident. As such, a sample of contaminated rice oil was stored in a cold dark place within our laboratory until analysis.

Analysis

The extraction and cleanup of PCBs in the blood samples were carried out according to a procedure described previously⁽⁶⁾⁽⁷⁾. Briefly, the extraction of lipids from 5 g, a portion of each blood samples was performed with an accelerated solvent extractor (ASE) system, and the extract was refined with a sulfuric acid treatment, a silver nitrate silica gel column and an activated carbon dispersed silica gel column cleanup, additionally a sulfoxide cartridge column as a further cleanup method. After cleanup, the sample was concentrated and transferred to an injection vial. On the other hand, the samples utilized for the analysis of PCBs in the rice oil were not subjected to extraction and cleanup. Briefly, 200 μ l of the rice oil was diluted with hexane to a total volume of 200 ml. A portion of the diluted sample was transferred to an injection vial. Additionally, a vial containing KC-mixtures standard (Kanechlor KC-300, 400, 500, 600, GL Sciences, Japan) was prepared, for comparison to the contaminated rice oil.

The measurement of PCBs was performed using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS). The measurement conditions were as follows : the gas chromatograph was an HP-6890 (Agilent Technologies, USA) equipped with an Autospec Ultima NT (Waters, USA) ; the column was a HT8-PCB fused silica capillary column, 0.25 mm i.d. \times 60 m (KANTO Chemicals, Japan) ; the column oven temperature was programmed to increase at a rate of 20°C min⁻¹ from an initial

Table 1 PCB concentrations in blood samples collected from patients during medical check-ups.

IUPAC#	Concentration (pg g ⁻¹ lipid)			IUPAC#	Concentration (pg g ⁻¹ lipid)		
	Yusho Patients (YP)		Normal Controls (NC)		Yusho Patients (YP)		Normal Controls (NC)
	2005(n=237)	2012(n=139)	2005(n=127)		2005(n=237)	2012(n=139)	2005(n=127)
	Mean	Mean	Mean		Mean	Mean	Mean
245-TrCB (#29)	32	16	25	22'33'46'-HxCB (#132)	188	128	282
244'-TrCB (#28)	1371	1428	2571	22'44'55'-HxCB (#153)	134448	128123	89821
344'-TrCB (#37)	19	426	-	22'3455'-HxCB (#141)	303	161	324
22'55'-TeCB (#52)	977	753	1290	22'344'5'-HxCB (#137)	6019	5497	2968
22'45'-TeCB (#49)	235	179	303	22'33'45'-HxCB (#130)	4466	3773	2620
22'44'-TeCB (#47)	438	342	605	23'3'4'5'6'-HxCB (#164)	27083	28766	19350
22'35'-TeCB (#44)	312	170	458	22'344'5'-HxCB (#138)	66117	57218	40872
23'4'6'-TeCB (#71)	87	27	192	22'33'44'-HxCB (#128)	865	673	876
23'4'5'-TeCB (#63)	84	79	146	23'44'55'-HxCB (#167)	3927	3788	3649
244'5'-TeCB (#74)	9835	9209	19472	23'3'44'5'-HxCB (#156)	30958	25632	7982
23'4'5'-TeCB (#70)	197	135	259	23'3'44'5'-HxCB (#157)	8418	6488	2024
23'44'-TeCB (#66)	1514	1582	2338	22'33'566'-HpCB (#179)	219	137	208
23'3'4'-/2344'TeCBs (#56/60)	489	282	884	22'33'55'6'-HpCB (#178)	9511	10297	6248
22'35'6'-PeCB (#95)	667	527	833	22'344'56'-HpCB (#182/187)	43375	42047	28083
22'355'-PeCB (#92)	601	530	860	22'344'5'6'-HpCB (#183)	10460	8087	6145
22'455'-PeCB (#101)	1680	1480	1898	22'344'56'-HpCB (#181)	315	159	71
22'44'5'-PeCB (#99)	17682	12882	12505	22'33'4'56'-HpCB (#177)	8533	8023	5753
23'4'56'-PeCB (#117)	1401	1076	927	22'33'455'-HpCB (#172)	5948	5909	2974
22'345'-PeCB (#87)	646	459	692	22'344'55'-HpCB (#180)	110380	113585	59481
22'344'-PeCB (#85)	142	118	218	23'3'44'5'6'-HpCB (#191)	1813	1467	766
23'3'4'6'-PeCB (#110)	365	231	411	22'33'44'5'-HpCB (#170)	39700	34771	17268
23'3'4'5'-PeCB (#107)	693	765	987	23'3'44'55'-HpCB (#189)	4542	4050	1052
2'344'5'-PeCB (#123)	276	194	466	22'33'55'66'-OcCB (#202)	4547	3870	2812
23'44'5'-PeCB (#118)	16343	17117	24353	22'33'45'66'-OcCB (#200)	663	351	648
2344'5'-PeCB (#114)	1895	1722	1697	22'33'4566'-OcCB (#201/198)	25584	9644	10093
23'3'44'-PeCB (#105)	3473	3484	5061	22'344'55'6'-OcCB (#203)	19357	9078	7820
22'355'6'-HxCB (#151)	1254	1027	1255	22'33'44'56'-OcCB (#195)	4389	3477	1820
22'33'56'-HxCB (#135)	470	312	475	22'33'44'55'-OcCB (#194)	19132	19268	8595
22'34'56'-HxCB (#147)	612	524	484	23'3'44'55'6'-OcCB (#205)	873	463	309
22'344'6'-HxCB (#139)	742	151	822	22'33'455'66'-NoCB (#208)	948	1048	775
22'33'56'-HxCB (#134)	25	10	27	22'33'44'566'-NoCB (#207)	414	323	339
23'3'55'6'-HxCB (#165)	1412	-	-	22'33'44'55'6'-NoCB (#206)	3088	2995	1960
22'34'55'-HxCB (#146)	21873	22521	13899	22'33'44'55'66'-DeCB (#209)	1153	760	1361
				Total PCBs	652325	619820	431955

- : not detected

temperature of 130°C (1 min hold) to 220°C, then at a rate of 3°C min⁻¹ to 280°C, and then at a rate of 20°C min⁻¹ to a final temperature of 300°C (3.5 min hold). The flow rate of the helium carrier gas was 1.3 ml/min (constant flow). The injection temperature was maintained at 280°C and the sample (2μl) was injected in splitless mode. The ionizing energy, accelerating voltage, and trap current were 38 eV, 8.0 kV, and 650μA, respectively. Analysis was performed using EI ionization and the selected ion monitoring mode. The resolution was maintained at 10000 at 5% valley.

Results and discussion

The concentrations of the major and specific PCB isomers in the blood collected from Yusho patients in 2005 and 2012 are shown in Table 1, including the data of normal controls previously reported⁸⁾. Among the 209 PCB isomers, 8 mono-*ortho* PCBs and 57 non-dioxin-like PCBs were identified in the blood of Yusho patients in 2012. The total concentrations of PCB isomers in the blood of Yusho patients in 2005 and 2012 were 652 and 620 ng g⁻¹ lipid, respectively. These results indicated that PCB concentrations in the blood of Yusho patients remained mostly un-

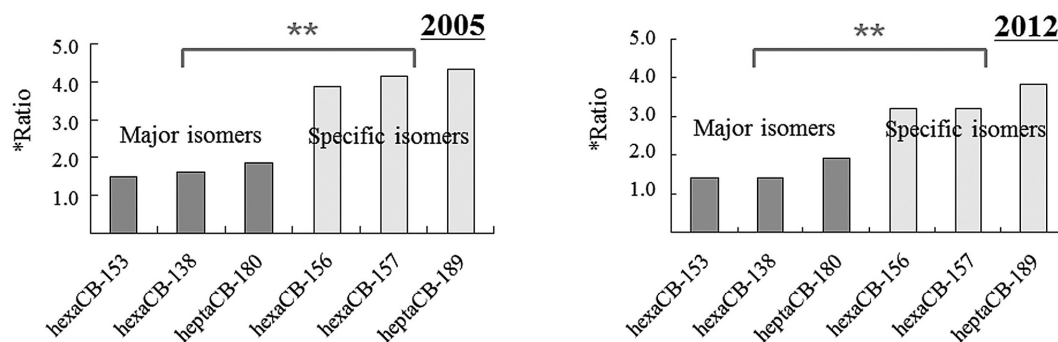


Fig. 1 Comparison of ratios of concentrations of major and specific PCB isomers.
 †Ratio = PCB concentrations of Yusho patients/those of the normal controls.
 ** $p < 0.01$; evaluated by Student's t-test.

changed for 7 years. The total concentrations were 1.4–1.5 times higher than those of the normal controls in 2005.

In this study, we focused on 6 isomers which are composed of hexaCB-153, hexaCB-138 and heptaCB-180 (major isomers), and hexaCB-156, hexaCB-157, and heptaCB-189 (specific isomers). HeptaCB-182/heptaCB-187 and heptaCB-181 were not targeted, because the former exhibited an overlapping peak, and the latter existed at a low concentration. The concentrations of hexaCB-153, hexaCB-138, and heptaCB-180 in the blood of Yusho patients were 134, 66, and 110 ng g⁻¹ lipid in 2005, and 128, 57, and 114 ng g⁻¹ lipid in 2012, as shown in Table 1. It was confirmed that hexaCB-153, hexaCB-138, and heptaCB-180 contributed to the total PCB concentrations in the blood of Yusho patients. In addition, these major isomers were also found at high concentrations in the blood of the normal controls (Table 1). The ratios relative to the normal controls ranged from 1.5–1.9; there were no significant differences between the concentrations of the isomers in the blood of Yusho patients and the normal controls, as shown in Fig. 1.

On the other hand, the concentrations of hexaCB-156, hexaCB-157, and heptaCB-189 in the blood of Yusho patients were 31, 8.4, and 4.5 ng g⁻¹ lipid in 2005, and 26, 6.5, and 4.1 ng g⁻¹ lipid in 2012, respectively. The concentrations of the specific isomers were lower than those of the major isomers, whereas the ratios of the specific

isomers were significantly higher than those of the major isomers (Fig. 1). The ratios of the concentrations of hexaCB-156, hexaCB-157, and heptaCB-189 to those of the major isomers in the blood of Yusho patients were 3.2–3.9, 3.2–4.2, and 3.8–4.3, respectively, and were higher than those of the normal controls. These results indicated that, even though more than 40 years have passed since the Yusho incident, Yusho patients contained higher concentrations of hexaCB-156, hexaCB-157, and heptaCB-189 in their blood than unaffected people.

The results led to two hypotheses regarding why specific isomers accumulated in the blood of Yusho patients. One possible interpretation was that the specific isomers were at high concentrations in the contaminated rice oil, and the other was that these were difficult to be metabolites such as OH-PCBs. Previous studies regarding contaminated rice oil from the Kanemi-Yusho incident focused on polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and non-*ortho* PCBs; however, the information regarding concentration of non-dioxin-like PCBs was not frequently reported. Therefore, we analyzed the concentrations of major and specific isomers in the contaminated rice oil from the incident. Notably, these isomers were detected at high concentrations in the rice oil. The concentrations of the major isomers hexaCB-153, hexaCB-138, and heptaCB-180 were 1800, 3500, and 1200 ng g⁻¹, respectively. On the other hand,

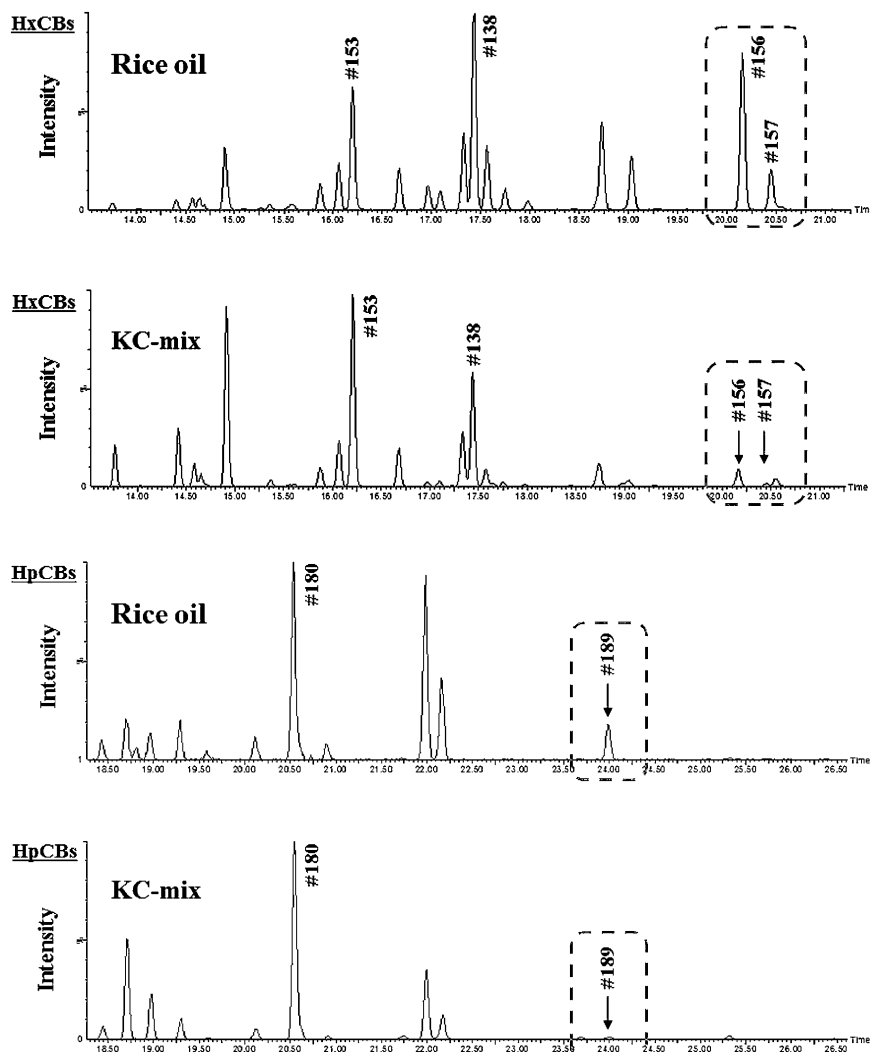


Fig. 2 Comparison of the chromatograms of PCB isomers in contaminated rice oil and KC-mixtures.

those of the specific isomers, hexaCB-156, hexaCB-157, and heptaCB-189 were 1800, 450, and 190 ng g^{-1} , respectively. The concentration pattern of these isomers was corresponded to a previous data⁹⁾. In particular, the concentration of hexaCB-156 was nearly as high as the concentrations of the major isomers. This concentration level was similar to a previous report on that of hexaCB-156 in the other contaminated rice oil¹⁰⁾. Thus, these findings demonstrated that the specific isomers in the contaminated rice oil remained at high concentration. In conclusion, it was considered to be one of the reasons that these isomers were highly accumulated in Yusho patients as compared to the normal controls.

Interestingly, in this study, the component fraction of the specific isomers in the rice oil was higher than that in the KC-mixtures which was common PCB products. A comparison of chromatograms is shown in Fig. 2, to illustrate the intensity of the specific isomers in the rice oil and KC-mixture. Major differences in the peak areas corresponding to hexaCB-156 and hexaCB-157 were noted, but minor differences in the peak areas corresponding to hexaCB-153 and hexaCB-138. Additionally, the amount of heptaCB-189 in the rice oil was greater than that in the KC-mixture. Therefore, these differences might be caused by the thermal metamorphism of PCBs, which were used as heat-transfer medium

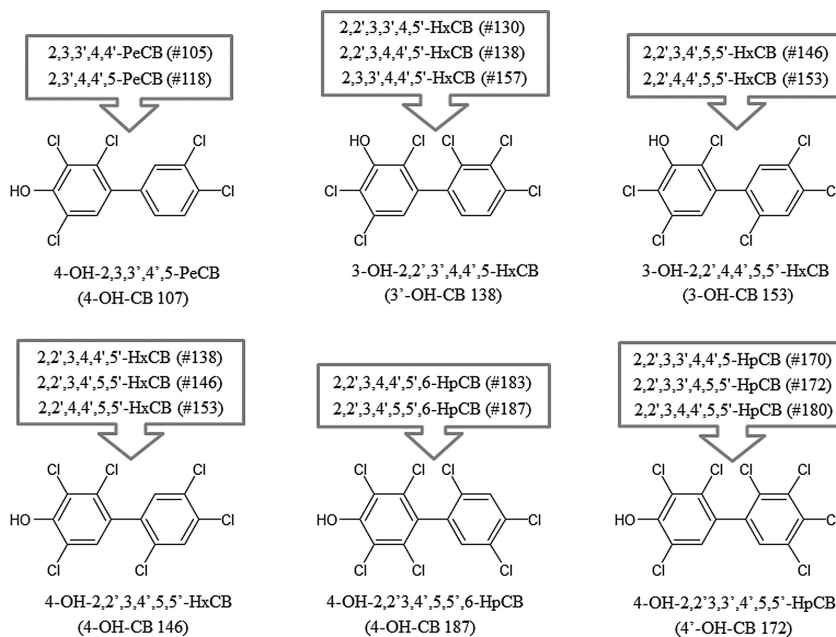


Fig. 3 Chemical structures of the common OH-PCBs and their parent PCBs in human blood.

in the process of rice oil production. Notably, previous studies regarding the formation of PCDF from PCB upon heating at a high temperature might imply a change in the PCB isomer pattern¹¹⁾¹²⁾.

As mentioned above, there were no significant differences in the ratios of the concentrations of the major isomers detected in the blood of Yusho patients to those in the normal controls, while hexaCB-153, hexaCB-138, and heptaCB-180 were highly detected in the rice oil (Fig. 1). This result clearly indicated that the accumulation of the specific isomers in humans was different from those of the major isomers. In other words, the rate of elimination of these compounds from the human body might have differed. Therefore, we investigated the metabolism of PCBs in order to verify this hypothesis. Several previous studies on the metabolism of PCBs showed that OH-PCBs are the main metabolites of PCBs, and are formed by the cytochrome P450 (CYP) monooxygenase enzyme system¹³⁾¹⁴⁾. The OH-PCBs are formed from direct electrophilic addition of oxygen or an arene oxide intermediate by hepatic CYP enzymes¹⁵⁾. Metabolic patterns of PCB isomers

were reported in animal studies^{15)–17)}. PCB isomers with a lower number of chlorine substitutions, including 2,3-, 2,5-, and 2,6-dichlorination or 2,3,6- trichlorination patterns, are easily metabolized to OH-PCBs. Additionally, PCB isomers with chlorines in the 4-, 3,4-, 3,5-, 2,4,5-, 2,3,4,6-, or 2,3,5,6- positions are slightly metabolized¹³⁾.

In this study, we found that specific PCB isomers hexaCB-156, hexaCB-157, and heptaCB-189 accumulated in the blood of Yusho patients. A review of previous research revealed that 4-OH-CB107, 3'-OH-CB138, 4-OH-CB146, 3-OH-CB153, and 4-OH-CB187 were commonly detected as PCB metabolites in the blood of humans from several countries¹³⁾. The above major OH-PCB isomers were also detected in the blood of Yusho patients¹⁸⁾¹⁹⁾. These OH-PCB isomers and their parent PCB compounds are shown in Fig. 3¹³⁾²⁰⁾. These findings imply that hexaCB-156, hexaCB-157, and heptaCB-189 are not easily metabolized in humans, although studies related to the metabolism of these PCB isomers are limited. As a result, the specific isomers might remain in the blood of Yusho

patients.

Finally, it is necessary to consider the intake of dietary PCBs from foods such as seafood. Hori et al. investigated the relationship between seafood consumption and accumulation of PCBs in humans²¹⁾. According to the report, intake of the specific isomers might be considerably low, because these isomers constitute less than 1% of PCB isomers. Therefore, it seems unlikely that intake of the specific isomers from foods is high. In conclusion, the specific isomers exposed at Yusho incident might remain in the patients for a long time ; consequently, these isomers were detected at higher concentrations in the blood of Yusho patients as compared to those in the normal controls.

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(和文抄録)

2012 年度油症認定患者の血液中に残留する ポリ塩素化ビフェニルに関する研究

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2012年に実施したカネミ油症検診において、油症患者から血液を採取して、PCB分析を実施した。その結果、患者における総PCB濃度の平均値は 620 ng g^{-1} (脂肪重量換算)であり、2005年の濃度結果とほぼ同等であった。本研究では、ヒト血液中から高濃度で検出される主要異性体 (hexaCB-153, hexaCB-138 及び heptaCB-180) と油症患者の血液から高濃度で検出される特定異性体 (hexaCB-156, hexaCB-157 及び heptaCB-189) に注目し、なぜ油症患者に特定異性体が残留しているのか、その原因について調査した。その結果、油症の原因となったライスオイルから、hexaCB-156, hexaCB-157 及び heptaCB-189 が、それぞれ $1800, 450, 190 \text{ ng g}^{-1}$ で検出され、これらの異性体が極めて高い濃度で含まれていることが明らかになった。また、PCBs 代謝に関する過去の研究報告から、特定異性体は主要異性体とは異なり、代謝されにくい構造を持つ物質であることが示唆された。以上のことから、油症発症から40年以上が経過した現在でも、特定異性体は油症患者の体内において高いレベルで残留していると考えられた。