PCB and PCDF Congeners in the Blood and Tissues of Yusho and Yu-Cheng Patients

by Yoshito Masuda,* Hiroaki Kuroki,* Koichi Haraguchi* and Junya Nagayama†

Polychlorinated biphenyl (PCB) poisonings occurred in western Japan, where it is called Yusho, in 1968, and in central Taiwan, where it is called Yu-Cheng, in 1979. The average concentrations of PCBs in the adipose tissue, liver, and blood of Yusho patients and in the blood of Yu-Cheng patients were 1.9 ppm, 0.08 ppm, 6.7 ppb and 99 ppb, respectively. Seven PCB congeners, such as 2,4,5,3',4'-pentachloro-, 2,3,4,3',4'-pentachloro-, 2,4,5,2',4',5'-hexachloro-, 2,3,4,2',4',5'-hexachloro-, 2,3,4,5,3',4'-hexachloro-, 2,3,4,2',5',5'-heptachloro- and 2,3,4,5,2',3',4'-heptachlorobiphenyls were identified in the blood and tissues of patients with Yusho and Yu-Cheng and controls. The concentration of 2,3,4,5,3',4'-hexachlorobiphenyl was comparatively higher in the patients than in controls. The concentrations of polychlorinated dibenzo-p-dioxins (PCDDs) in the adipose tissue and liver of Yusho patients were 6 to 13 ppb and 3 to 25 ppb, respectively, while no PCDFs were detected in the controls. Major PCDF congeners identified in the tissues and blood of Yusho and Yu-Cheng patients were 2,3,6,8-tetrachloro-, 2,3,7,8-tetrachloro-, 1,2,4,7,8-pentachloro-, 2,3,4,7,8-pentachloro- and 1,2,3,4,7,8-hexachlorodibenzofurans (DFs), of which the 2,3,4,7,8-pentachloro compound was predominant. The concentrations of methylthio-PCB in the liver, lung and adipose tissue of Yusho patients were 0.1 to 0.5, 0.2 to 1.4 and 0.5 to 1.0 ppb, respectively, and those of methylylthion-PCBs were 0.3 to 0.7, 1.0 to 2.5 and 0.7 to 1.0 ppb, respectively. Some of the major peaks of the PCB methylthio and methylylsulfone derivatives were identical in gas chromatographic retention times with those of 4-methylthiobiphenyl and 4-methylsulfone-2,5,2',5'-tetrachlorobiphenyl PCDFs, especially 2,3,4,7,8-pentachloro DF, appear to be mainly responsible in the poisonings.

Introduction

Ingestion of rice oil contaminated with polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated quaterphenyls (PCQs) caused mass food poisoning called Yusho in western Japan in 1968 (1-3) and Yu-Cheng in central Taiwan in 1979 (4). Yusho patients totaled 1788 at the end of 1982 and 2060 for Yu-Cheng in the beginning of 1983. They suffered from various chronic symptoms, such as acen-form eruptions, hypersecretion of the Meibomian glands, hyperpigmentation of the face, eyelids, gingiva, nails and mucous membrane, abdominal pain, headache, and general fatigue (5).

This paper describes PCB and PCDF congeners and sulfur-containing metabolites of PCBs retained in the blood and tissues of Yusho and Yu-Cheng patients and then discusses the relationship between these congeners and the etiology of symptoms of Yusho and Yu-Cheng.

PCBs

Blood and autopsy tissues from the patients with Yusho were analyzed for PCBs by saponification in 1N NaOH ethanol solution, extraction with n-hexane, column chromatography on silica gel, and then gas chromatography with electron capture detection. The concentrations (mean ± SD) of PCBs in the adipose tissue, liver and blood of Yusho patients about 5 years after the outbreak (6,7) were 1.9±1.4 ppm (N = 9), 0.08 ± 0.06 ppm (N = 8) and 6.7 ± 5.3 ppb (N = 41), respectively. These values were only about twice those of controls. The blood PCB level of some of Yu-Cheng patients was 99 ± 163 ppb (N = 23) (8) and much higher than that of PCBs from the Taiwanese population (1.2 ± 0.7 ppb, N = 29) and the value of Yusho patients described above. The difference in PCB levels in Yusho...
and Yu-Cheng patients is probably due to the timing of sampling, being about 5 years after exposure for Yusho and 1 year for Yu-Cheng. The PCB fractions from the blood of Yusho and Yu-Cheng patients were also gas chromatographed on an efficient Apiezon L column (5 m) to identify main PCB congeners in the blood. Figures 1 and 2 show gas chromatograms of PCBs from the adipose tissue and blood of Yusho and Yu-Cheng patients. Individual peaks were identified for PCB structures by comparing their retention times with those of authentic PCB congeners and by obtaining their spectra by gas chromatography-mass spectrometry (8,9). The structures of individual PCBs and their concentrations in the blood of Yusho and Yu-Cheng patients are listed in Table 1. The concentrations of individual PCBs in the blood were characteristically different between Yusho patients and normal persons. In the blood of Yusho patients, the concentration of 2,4,5,3',4'-pentachlorobiphenyl, corresponding to peak 1, was lower than that of normal persons, while the concentration of 2,3,4,5,3',4'-hexachlorobiphenyl, corresponding to peak 5, was higher. This characteristic difference in gas chromatographic pattern has been

![Gas chromatograms of PCBs on 1.5% Apiezon L column (5 m): (A) from adipose tissue of Yusho patient; (B) from adipose tissue of nonexposed control; (C) sample of Kanechlor 600. PCB structures of the numbered peaks are given in Table 1. Data of Kuroki and Masuda (9).](image)

**Figure 1.** Gas chromatograms of PCBs on 1.5% Apiezon L column (5 m): (A) from adipose tissue of Yusho patient; (B) from adipose tissue of nonexposed control; (C) sample of Kanechlor 600. PCB structures of the numbered peaks are given in Table 1. Data of Kuroki and Masuda (9).

![Gas chromatograms of PCBs on 1.5% Apiezon L column (5 m): (A,B) from the blood of Yu-Cheng patients; (C) sample of Kanechlor 500. PCB structures of the numbered peaks are given in Table 1. Data of Masuda et al. (8).](image)

**Figure 2.** Gas chromatograms of PCBs on 1.5% Apiezon L column (5 m): (A,B) from the blood of Yu-Cheng patients; (C) sample of Kanechlor 500. PCB structures of the numbered peaks are given in Table 1. Data of Masuda et al. (8).

**Table 1. Concentrations of PCB congeners in the blood of patients with Yusho and Yu-Cheng (Fukuoka and Taiwan).**

| Peak no. | PCB assigned | Fukuoka, control (N = 7) | Fukuoka, Yusho patient (N = 9) | Fukuoka, Yu-Cheng patient (N = 10) | Taiwan, Yusho controls | Taiwan, Yu-Cheng controls |
|----------|--------------|--------------------------|-----------------------------|-------------------------------|--------------------------|--------------------------------|
| 1        | 2,4,5,3',4'  | 0.22 ± 0.09              | 0.13 ± 0.05                 | 3.46 ± 2.37                   | 0.59                     | 16                             |
|          | Penta-CB     |                          |                             |                               |                          | 27                             |
| 2        | 2,3,4,3',4'  | 0.05 ± 0.02              | ND^b                        | 1.20 ± 1.03                   | —                        | 24                             |
|          | Penta-CB     |                          |                             |                               |                          | —                              |
| 3        | 2,4,5,2',4',5' Hexa-CB | 0.15 ± 0.07              | 0.52 ± 0.22                 | 2.51 ± 0.96                   | 3.5                      | 17                             |
|          |              |                          |                             |                               |                          | 4.8                            |
| 4        | 2,3,4,2',4',5' Hexa-CB | 0.17 ± 0.07              | 0.65 ± 0.21                 | 4.66 ± 1.43                   | 3.8                      | 27                             |
|          |              |                          |                             |                               |                          | 7.2                            |
| 5        | 2,3,4,5,3',4' Hexa-CB | 0.04 ± 0.02              | 0.28 ± 0.07                 | 1.79 ± 0.69                   | 7.0                      | 45                             |
|          |              |                          |                             |                               |                          | 6.4                            |
| 6        | 2,3,4,5,2',4',5' Hepta-CB | 0.12 ± 0.07              | 0.44 ± 0.15                 | 1.73 ± 0.63                   | 3.7                      | 14                             |
|          |              |                          |                             |                               |                          | 3.9                            |
| 7        | 2,3,4,5,2',3',4' Hepta-CB | 0.11 ± 0.04              | 0.28 ± 0.09                 | 1.18 ± 0.45                   | 2.5                      | 11                             |
|          |              |                          |                             |                               |                          | 4.2                            |
|          |              |                          |                             |                               |                          |                                |
| Total    |              | 0.86                     | 2.3                         | 16.53                         | 2.7                      | 19                             |

^aMean ± SD

^bND = not detected<0.01 ppb.
adopted as one of the criteria for diagnosis of Yusho (10). In the blood of Yu-Cheng patients, the concentration of 2,4,5,3',4'-pentachlorobiphenyl was relatively high, as shown in Figure 2. However, its concentration gradually decreased with time, changing its gas chromatographic pattern to that of typical Yusho. Relatively high concentrations of 2,3,4,5,3',4'-hexachlorobiphenyl were observed in the blood of Yu-Cheng patients (Table 1).

According to the biological activity tests in the rats pretreated with PCB congeners (11), of the PCB congeners identified in the patients, 2,3,4,5,3',4'-hexachlorobiphenyl showed the highest enzyme-inducing activity on benzo[a]pyrene hydroxylase and DT-diaphorase in the rat liver homogenates and caused most of the marked atrophy of the thymus and hypertrophy of the liver in the rats.

Considering the high accumulation in the patients and the strong biological activity, 2,3,4,5,3',4'-hexachlorobiphenyl is the PCB congener most closely correlated with the occurrence of symptoms of Yusho and Yu-Cheng.

**PCDFs**

The adipose tissue and liver of deceased Yusho patients were analyzed for PCDFs by gas chromatography with electron capture detection after the separation of PCBs and PCDFs by column chromatography on alumina. The individual gas chromatographic peaks were confirmed to be PCDFs by gas chromatography–mass spectrometry as shown in Figure 3 and mass fragmentography. The concentrations of PCDFs in the adipose tissue and liver were in ranges of 6 to 13 and 3 to 25 ppb, respectively. No PCDFs were detected at the detection limit of 0.005 ppb in the same tissues obtained at autopsy from persons who had been killed in traffic accidents (12). The PCDF concentrations in the adipose tissue and liver of Yusho patients were on similar levels, whereas the concentration of PCBs in the adipose tissue was more than ten times that in the liver. These results indicate that PCDFs are more retainable in the liver than PCBs.

The PCDF fractions separated from the tissues of Yusho patients were further determined by gas chromatography and mass fragmentography with more efficient columns for identifying PCDF congeners. A glass column (5 m) packed with 1.5% Apiezon L (13) and a fused silica capillary column coated with OV-101 (Fig. 4) were used for the gas chromatography, and a glass capillary column coated with OV-17 was for the mass fragmentography (14). Individual PCDF congeners were identified by comparing their retention times with those of corresponding authentic PCDF congeners. Table 2 lists the concentrations of PCDF congeners in the adipose tissue and liver of Yusho patients. Among the several PCDF congeners identified, 2,3,7,8-tetrachlorodibenzofuran (DF) was determined to be at low levels, while 2,3,4,7,8-pentachloro-DF was predominant even in the tissues of the patient who died 9 years after the outbreak (13). The adipose tissue and liver of a baby who was born to a mother with Yu-Cheng and the blood of Yu-Cheng patients were also analyzed for PCDF congeners by mass fragmentography (15). The results are summarized in Table 3. Similar to the PCDF congeners in Yusho patients, relatively low concentration of 2,3,7,8-tetrachloro-DF and high concentrations

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**Figure 3.** Gas chromatography–mass spectra of PCDF fractions: (A, C) tissue from liver of Yusho patients; (B) synthesized PCDFs; (D) sample of contaminated rice oil.

**Figure 4.** Gas chromatogram of PCDF fraction of tissue from the liver of a Yusho patient. Column: fused silica capillary coated with OV-101, 5 m; oven temperature, 180–250°C; rate of rise 2°C/min; electron capture detector.
of 2,3,4,7,8-pentachloro-DF and 1,2,3,4,7,8-hexachloro-DF were also observed in the Yu-Cheng patients, although the high concentration of 1,2,3,7,8-pentachloro-DF in Yu-Cheng patients was in contrast with its low concentration in Yusho patients.

About 40 PCDF congeners were identified in the rice oil which was ingested by Yusho patients (16). Some of them, such as 2,3,6,7-tetrachloro-, 2,3,4,6,7-pentachloro-, 1,2,6,7,8-pentachloro-, 1,2,3,4,7,8-pentachloro-, and 1,2,3,4,6,7-hexachloro-DF, were, however, not identified in the tissues of the patients. These congeners were relatively easily metabolized and excreted, since they have two adjacent carbon atoms not substituted with chlorine atoms in the dibenzofuran ring. In contrast with these congeners, the PCDF congeners retained in the body for a long time, such as 2,3,6,8-tetrachloro-, 2,3,7,8-tetrachloro-, 1,2,4,7,8-pentachloro-, 2,3,4,7,8-pentachloro-, and 1,2,3,4,7,8-hexachloro-DF, do not have such adjacent carbon atoms (14).

The individual PCDF congeners identified in the patients with Yusho and Yu-Cheng were synthesized and purified by recrystallization and/or high performance liquid chromatography and subjected to tests of biological activity and retention. Most of the PCDF congeners showed strong enzyme-inducing activities on benzo(a)pyrene hydroxylase and DT-diaphorase and caused severe atrophy of the thymus and significant hypertrophy of the liver in the treated rats (17,18). Above all, a dose–response study of 2,3,4,7,8-pentachloro-DF, the PCDF congener retained to the highest extent in patients with Yusho and Yu-Cheng, demonstrated that the minimum dosages of this congener were 1 μg/kg for the inductive effects and 10 μg/kg for gravimetric changes of the tissues (17). The high accumulating tendency of 2,3,4,7,8-pentachloro-DF in the liver of the patients was also confirmed by animal experiments in rats and monkeys (19). Considering all these aspects, we cannot disregard these PCDFs, especially 2,3,4,7,8-pentachloro-DF, as the most important etiologic agents for symptoms of Yusho and Yu-Cheng.

### Sulfur-Containing Metabolites of PCBs

Methylsulfone metabolites of PCBs are known to be persistent compounds in the tissues of humans and animals (20,21). Therefore, liver, lung, and adipose tissue of Yusho patients was analyzed for methylthio and methylsulfone derivatives of PCBs by gas chromatography, gas chromatography–mass spectrometry and mass fragmentography after column chromatography.

### Table 2. Concentrations of PCBs and PCDF congeners in the liver and adipose tissue of Yusho patients. 

| Case | Time of death | Tissue | Concentration of PCBs, ppm | Concentration of PCDFs (ppb) | Ratio PCBs/PCDFs × 100 |
|------|---------------|--------|---------------------------|----------------------------|------------------------|
|      |               |        | A  | B  | C  | D  | E  | Total |                  |
| 1    | July 1969     | Liver  | 0.14 | 0.7 | 0.3 | 7.1 | 6.9 | 2.6 | 17.6 | 13 |
| 2    | July 1969     | Liver  | 0.2  | 0.08 | 0.02 | 0.4 | 1.2 | 0.3 | 2.0 | 1  |
| 3    | May 1972      | Liver  | 2.8  | 2.8  | 0.3  | 1.0 | 5.7 | 1.7 | 9.3 | 0.3 |
| 4    | April 1975    | Adipose| 0.08 | 0.08 | ND  | 0.2 | 0.8 | 0.2 | 1.28 | 0.03 |
| 5    | March 1977    | Liver  | 0.006 | ND  | ND  | 0.02 | 0.1 | 0.04 | 0.16 | 2.7 |

*Data of Kuroki and Masuda (13).
*Compounds: (A) 2,3,6,8-tetrachloro-DF; (B) 2,3,7,8-tetrachloro-DF; (C) 1,2,4,7,8-pentachloro-DF; (D) 2,3,4,7,8-pentachloro-DF; (E) 1,2,3,4,7,8-hexachloro-DF.
*ND = not detected (<0.005 ppb).

### Table 3. Concentration of PCBs and PCDF congeners in the tissues of Yu-Cheng infant and the blood of Yu-Cheng and Yusho patients.

|       | Baby | Yu-Cheng | Yusho, blood |
|-------|------|----------|--------------|
|       | Adipose tissue | Liver | Patient A | Patient B | Patient A | Patient B |
|       | Total PCBs, ppb | | | | | |
| 2,3,7,8-Tetrachloro-DF, ppt | 316 | 27 | 740 | 310 | 4 | 5 |
| 1,2,4,7,8-Pentachloro-DF, ppt | 17 | 60 | <30<sup>b</sup> | <30<sup>b</sup> | <30<sup>b</sup> | <30<sup>b</sup> |
| 1,2,3,7,8-Pentachloro-DF, ppt | 14 | 42 | 60 | 40 | ND<sup>c</sup> | ND |
| 2,3,4,7,8-Pentachloro-DF, ppt | 44 | 194 | 30 | 20 | ND | ND |
| 1,2,3,4,7,8-Hexachloro-DF, ppt | 68 | 91 | 120 | 80 | 3 | 3 |
| Total PCDFs, ppt | 131 | 193 | 150 | 60 | <6<sup>b</sup> | <6<sup>b</sup> |

*Rappe et al. (15).
*Less than detection limit.
*ND = not detected.
on silica gel, partition between $n$-hexane and sulfuric acid and high performance liquid chromatography (22). The methylthio-PCB fraction showed two peaks on gas chromatography and mass fragmentography corresponding to methylthio PCB derivatives. One of the two peaks was identical in retention time with that of 4-methylthio-2,5,2',5'-tetrachlorobiphenyl. Gas chromatography, gas chromatography–mass spectrometry and mass fragmentography of the methylsulfone PCB fractions showed at least 16 peaks corresponding to methylsulfone PCBs with three to six chlorine atoms. Some of the mass spectra are shown in Figure 5. One of the major peaks was assigned to 4-methylsulfone-2,5,2',5'-tetrachlorobiphenyl by the retention times in gas chromatography and mass fragmentography.

As summarized in Table 4, the levels of methylthio chlorinated biphenyls in the liver, lung and adipose tissue of Yusho patients were 0.1 to 0.5, 0.2 to 1.4 and 0.5 to 1.0 ppb, respectively, and those of the methylsulfone PCBs were 0.3 to 0.7, 1.0 to 2.5 and 0.7 to 1.0 ppb, respectively. The levels of methylthio and methylsulfone PCBs to that of PCBs were, therefore, 1 to 2% in the liver, 4 to 8% in the lung and 0.1 to 0.2% in the adipose tissue. The sulfur-containing metabolites of PCBs tended to accumulate more readily in the lung and liver than in the adipose tissue. The methylthio and methylsulfone PCBs present in the tissues of the patients should be studied to assess their toxic potencies and to evaluate the connection of these compounds with the symptoms of Yusho.

**Discussion**

The PCB level in the blood of Yusho patients was 6.7 ppb, on the average, only about twice that of controls. Some workers occupationally exposed to PCBs had

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**Table 4. Levels of PCBs, methylthio-PCBs and PCB-methylsulfones in the liver, lung and adipose tissue of Yusho patients and controls.**

| Case | Tissue | PCBs, ppb | Methylthio PCBs, ppb | PCB-methylsulfones, ppb | PCB + PCB-methylsulfones: PCBs ($\times 100$), % |
|------|-------|-----------|---------------------|------------------------|-----------------------------------------------|
| 1    | Liver | 45        | 0.5                 | 0.4                    | 2.0                                           |
|      | Lung  | 66        | 1.4                 | 1.1                    | 3.8                                           |
|      | Adipose | 880     | 0.5                 | 0.7                    | 0.1                                           |
| 2    | Liver | 100       | 0.5                 | 0.7                    | 1.2                                           |
|      | Lung  | 18        | 0.4                 | 1.0                    | 7.7                                           |
|      | Adipose | 2170   | 1.0                 | 0.8                    | 0.1                                           |
| 3    | Liver | 38        | 0.1                 | 0.3                    | 1.4                                           |
|      | Lung  | 56        | 0.2                 | 2.5                    | 4.8                                           |
|      | Adipose | 970    | 1.0                 | 1.0                    | 0.2                                           |
| Controls |       |         |                     |                        |                                               |
| 4    | Liver | 9         | ND*                 | 0.05                   | 0.6                                           |
|      | Lung  | 7         | 0.07                | 0.2                    | 3.9                                           |
|      | Adipose | 160    | ND                  | 0.2                    | 0.1                                           |
| 5    | Liver | 56        | ND                  | 0.04                   | 0.07                                          |
|      | Lung  | 18        | 0.05                | 0.9                    | 5.2                                           |
|      | Adipose | 180    | ND                  | 0.05                   | 0.03                                          |

*ND = not detected (<0.01 ppb).

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**Figure 5.** Gas chromatography-mass spectra of PCB methylsulfone fractions: (A.C) tissues from the lung of Yusho patients; (B) 2,5,4'-trichlorobiphenyl-4-methylsulfone, (D) 2,5,2',5'-tetrachlorobiphenyl-4-methylsulfone.
more than 100 ppb of PCBs in the blood (23). However, the workers showed no typical symptoms of Yusho or mild and benign clinical signs, while the patients with Yusho have been suffering from various Yusho symptoms for more than 15 years. This discrepancy cannot be fully explained by the difference in the blood PCB levels among the Yusho patients, occupationally exposed workers and nonexposed controls.

PCDF congeners were definitely identified in the blood and tissues of Yusho and Yu-Cheng patients, while no PCDFs were detected in the tissues of normal persons (12–15). These PCDF congeners, especially 2,3,4,7,8-tetrachloro-DF were highly likely to accumulate in the liver of humans, monkeys and rats and showed severe toxicity, producing atrophy of the thymus, hypertrophy of the liver and strong enzyme-inducing activities even at very low doses (1–10 \( \mu g/kg \)) (17–19). By an epidemiological study of the consumption of the rice oil by the patients with Yusho and the levels of PCDFs in the oil, the patients were calculated to have consumed 3.4 \( mg \) of PCDFs, on the average (24), corresponding to a PCDF intake of 68 \( \mu g/kg \) on assuming the average body weight to be 50 kg. The total PCDF intake is therefore considered to be enough to cause some symptoms of Yusho. The PCDF congeners ingested by the patients would be mainly responsible in the poisonings of Yusho and Yu-Cheng.

In evaluating causal agents for Yusho, polychlorinated quaterphenyls (PCQs) should be taken into consideration, because PCQs were ingested by the patients with Yusho and Yu-Cheng at levels comparable with PCBs (23–24). However, PCQs might not be important causal agents to develop the symptoms of Yusho and Yu-Cheng (23). Further study is necessary to clarify this relationship.

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