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Surveys of Workers Occupationally Exposed to PCBs and of Yusho Patients

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Surveys of workers occupationally exposed to polychlorinated biphenyls (PCBs) in the production of thread or of paint, and of Yusho patients were carried out from 1973 to 1982. PCB concentrations in the plasma of the workers ranged from 2 to 521 ppb, and some showed higher PCB levels in the plasma than typical Japanese Yusho patients. Gas chromatographic patterns of plasma PCBs of the workers with high PCB levels were shown to match the patterns of the PCBs to which they had been exposed in the workplace. Japanese Yusho children showed remarkable decrease with time, but no such decrease was observed in the Yusho adults and the workers.

Polychlorinated quaterphenyls (PCQs) were detected in the blood of typical Japanese and Taiwanese Yusho patients, but PCQ levels in the plasma of the workers were below the detection limit of 0.02 ppb.

Clinical findings and subjective complaints of the workers were usually slight compared with typical Yusho patients, though some of them had mild dermal manifestations and their PCB levels were suspected to be related to serum triglyceride values.

On the basis of these results, we discussed the relationship between the health status of the subjects and their contamination with PCBs or related compounds.

Introduction

Polychlorinated biphenyls (PCBs) were widely used in various industries in Japan because of their high chemical stability. Environmental and biological pollution due to PCBs used during a period of about 20 years has been widely reported, though the production of PCBs was prohibited in 1972 in Japan (*1–3*).

As we reported in our previous paper (*4*), an elderly man with no history of Yusho had been found by chance to have a very high level of PCBs (230 ppb in the plasma and 140 ppm in the adipose tissue on fat basis) when he underwent a laparotomy. His family was engaged in the production of silk thread for Nishijin-ori, a traditional silk fabric of Kyoto in Japan, and we found that the other persons in his family and an employee also had very high level of PCBs in the plasma though they had no history of Yusho. The PCB contamination was suspected to be of occupational or dietary origin, and was subsequently revealed to be of occupational origin, because high levels of PCBs with the similar gas chromatographic pattern as Kanechlor 500 (KC-500), a brand name of PCBs with chlorine content of 55%, was detected, in cooperation with Fujiwara (*3*), in samples taken from the floor, the soil under the machines, and the air of the workplace. The source was proven to be a reeling machine oil that had been used by the workers who were not aware that the oil contained PCBs. Therefore, we carried out a survey of similar kinds of workplaces in Kyoto and other districts. Moreover, we examined workers engaged in manufacturing marine paint who had been exposed to Kanechlor 600 (KC-600), a brand name of PCBs with chlorine content of 6 (60%), used from 1966 to 1972 as a material to increase the durability of paint.

This paper addresses the following questions: (1) What is the level of contamination with PCBs and related compounds in the workers occupationally exposed to KC-500 or KC-600, and in Yusho patients? (2) What is their health status? (3) Are there any differences in contamination or health status between these workers and Yusho patients? (4) What are the temporal changes in level and gas chromatographic pattern of their blood PCBs?

Materials and Methods

Materials

Blood samples were obtained from three groups of occupationally exposed workers, two groups of Yusho patients and two control groups.

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Subjects Occupationally Exposed to PCBs. Group A, consisting of 63 workers engaged in the production of silk thread for Nishijin-ori, were tested in 1974–1975, and some workers with high PCB levels and the two families were tested repeatedly from 1975 to 1982.

Group B, consisting of 42 workers engaged in the production of silk or wool thread in the cities of Kanazawa and Ichinomiya, Japan, were tested in 1975.

Group C, consisting of seven workers manufacturing marine paint were tested in 1976 and 1982.

Yusho Patients. Group D, consisting of 23 typical Yusho patients in Fukuoka Prefecture of Japan were tested in 1975–1977, and one family was repeatedly tested from 1973 to 1982.

Group E, consisting of eight patients suffering from PCB poisoning in Taichung, Taiwan, in 1980, considered to be similar to Yusho in Japan, were tested in 1980–1981.

Controls. Two groups of controls, group F, 24 normal persons in rural or urban regions of Fukuoka Prefecture, Japan, were tested in 1975–1977 and group G, 40 normal persons from the same area as group F, were tested in 1979–1980.

Extraction and Clean-up

For the extraction of PCBs from blood samples and their clean-up, the method of Jensen (*5*) with several modifications was used until 1978. The details of the analytical method were described in a previous paper (*6*). Blood samples obtained in 1979 and later were analyzed according to the method of Kashimoto et al. (*7*) to determine not only PCBs but also related compounds, i.e., PCQs (polychlorinated quaterphenyls) and PCDFs (polychlorinated dibenzofurans).

Gas Chromatographic Analysis

Gas chromatographic analysis was performed using a Shimadzu 4BM or 5A equipped with a ^{63}Ni electron capture detector. Gas chromatographic conditions were as follows. For analysis of PCBs: 1.5% SE-30 on Chromosorb W (60–80 mesh); glass column, 3 mm ID × 2 m, column temperature, 200°C; detector, 230°C; or 2% OV-1 on Gas Chrom Q (80–100 or 100–120 mesh); glass column, 2 mm ID × 1.8 m; column temperature 200°C; detector, 230°C.

For detailed qualitative analysis of PCBs: 2% Apiezon L on Varaport 30 (100–120 mesh); glass column, 2 mm ID × 5 m; column temperature, 250°C; detector, 270°C.

Nitrogen was used as a carrier gas. PCB concentrations were calculated based on one of the official calculation methods for PCBs in Japan (*8*), i.e., the total height of the main peaks with retention times longer than *p,p'*-DDE. The detailed PCB patterns of some blood samples were examined by analyzing the respective components of the PCBs, by using the 2% Apiezon L column, as reported by Jensen and Sundstroem (*9*). The Kanechlor series of PCBs were used for standards. The numbering of PCB peaks and analysis of PCB patterns on the 2% OV-1, 1.5% SE-30 and 2% Apiezon L column followed the method of Ugawa et al. (*10*) and Nakamura and Kashimoto (*11*), respectively.

The quantitative analyses of PCQs and PCDFs were performed according to the method reported by Kashimoto et al. (*7*).

Medical Examinations

Subjective complaints, clinical findings, triglyceride and total cholesterol values, hepatic function and so forth were investigated in 19 subjects of group A in 1977 and 13 of the 19 subjects in 1982, and in all of group C in 1976 and 1982 (excluding serum biochemical tests in 1982). As for group D, data from the periodic health examinations for Yusho in 1979 were used.

Results

PCB Concentration in Plasma

Distribution of PCB concentrations of groups A–F is described in Figure 1. Groups A–D showed significantly higher levels of PCBs than group F ($p < 0.01$). Some subjects belonging to groups A–C showed especially high levels of PCBs. Twelve of the 63 subjects in group

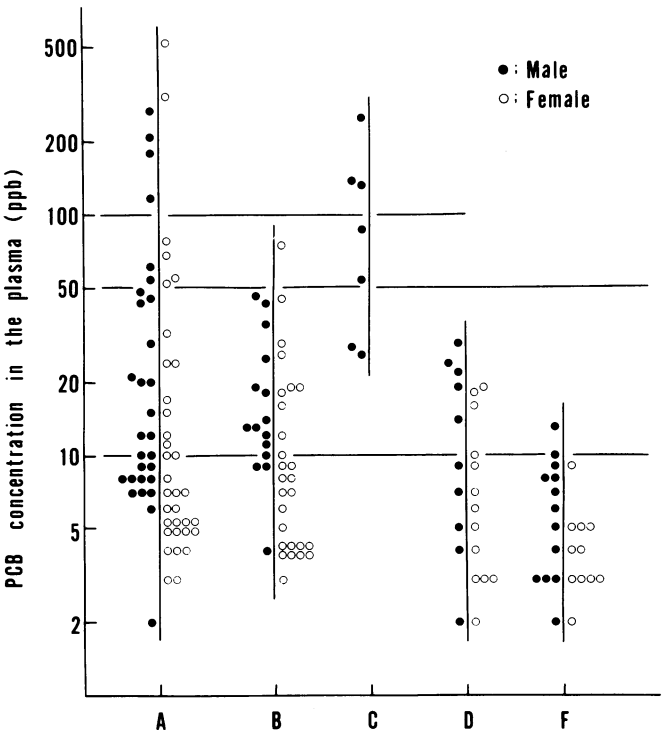

FIGURE 1. Distribution of PCB concentrations of groups A–F: (A) workers engaged in the production of silk thread for "Nishijin-ori" in Kyoto (1974–1975); (B) workers engaged in the production of silk or wool thread in the cities of Kanazawa and Ichinomiya (1975); (C) workers making marine paint in Osaka (1976); (D) typical Yusho patients in Fukuoka Prefecture (1975–1977); (F) normal persons in Fukuoka Prefecture (1975–1977).

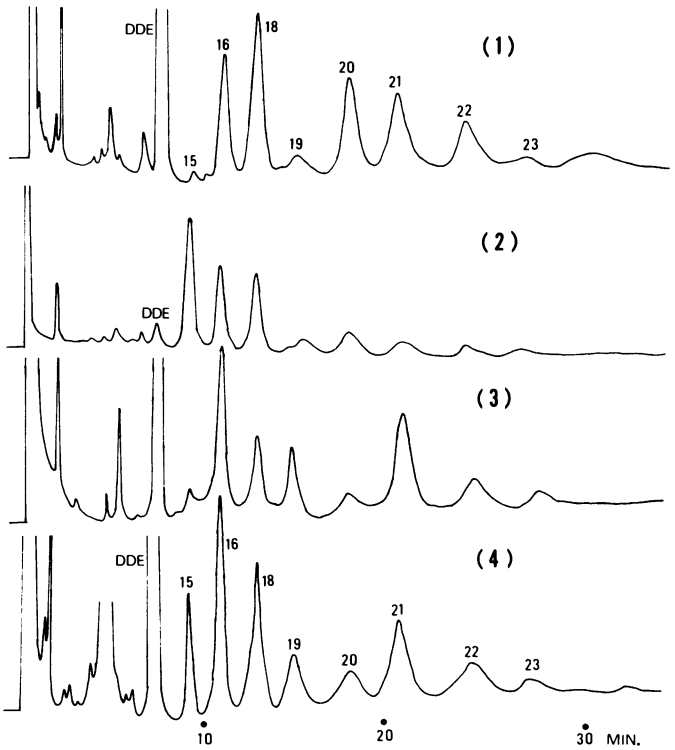

FIGURE 2. Gas chromatograms of PCBs in the plasma: (1) typical Japanese Yusho patient in group D; (2) worker engaged in the production of silk thread in group A; (3) worker making paint in group C; (4) normal person in group F. A SE-30 column was used.

A and five of the seven subjects in group C showed levels higher than 50 ppb, a level which was not observed in groups D and F. In group A, we analyzed the relationship between the PCB levels and the kind of job assigned to respective subjects or the length of service. The subjects with long terms of service who were engaged in the operation of silk reeling machines and related tasks showed a tendency to have high PCB levels. From this result, the origin of the PCB contamination was suspected to be the oil used in the silk reeling machines. We analyzed the old oils that had been used in the past and the oil being used at the time of survey at different workplaces in Kyoto. Consequently, PCB concentrations of from 8 to 10,000 ppm were found in the old oils, but no PCBs were present in the oils in current use. In Ichinomiya and Kanazawa, machine oils were also contaminated with PCBs.

The PCB level of a 13-year-old child of a female worker with a PCB level of 521 ppb in group A was also determined to be 179 ppb. Because the child was breast-fed, the origin of PCB contamination of the child was suspected to be the mother's milk. The 13- and 15-year-old children breast-fed by another female worker with a PCB level of 81 ppb were also examined and their levels determined to be 49 and 76 ppb, respectively. Therefore, the history of PCB exposure in the workers was considered to be very long, resulting in PCB contamination not only in the workers but also in their children.

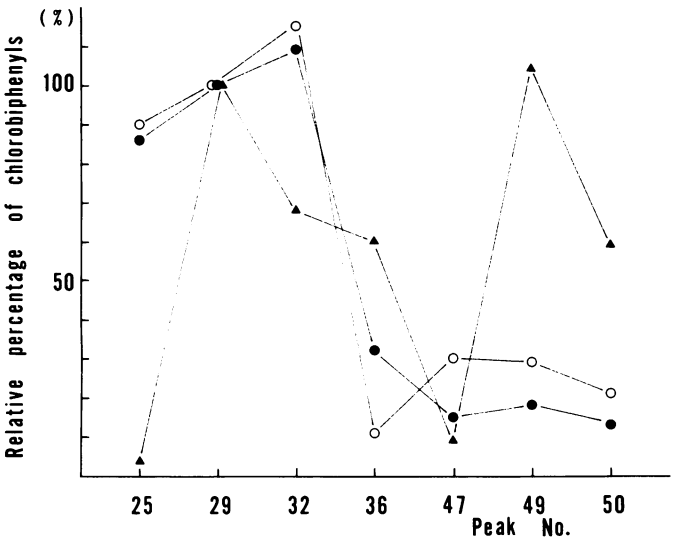

FIGURE 3. Relative percentages of respective PCB components of KC-500, KC-600 and mean of four subjects with high PCB levels, group A: (●) KC-500; (▲) KC-600; (○) group A. Apiezon L column was used.

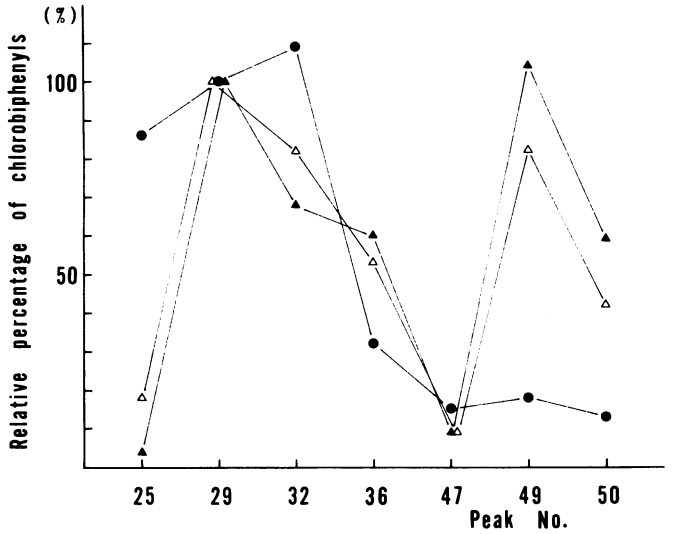

FIGURE 4. Relative percentages of respective PCB components of KC-500, KC-600 and mean of group C: (●) KC-500; (○) KC-600; (▲) group C. Apiezon L column was used.

Pattern Analysis of PCBs

Figure 2 shows the gas chromatograms of PCBs in the plasma. Remarkable characteristics compared with control were observed: i.e., peak 15 is low, and peak 20 is high in group D; peak 15 is high, and peak 21 is low in group A; peak 15 is low, and peak 21 is high in group C. To examine these characteristics in detail, we analyzed the respective components of the PCBs. The mean of the relative percentages of the PCB components of the seven main peaks (the component of peak 29 = 100%) of groups A and C were compared with KC-500 and KC-600. The PCB pattern of group A was similar to the KC-500 pattern (Fig. 3), while that of group C was similar to the KC-600 pattern (Fig. 4). These results

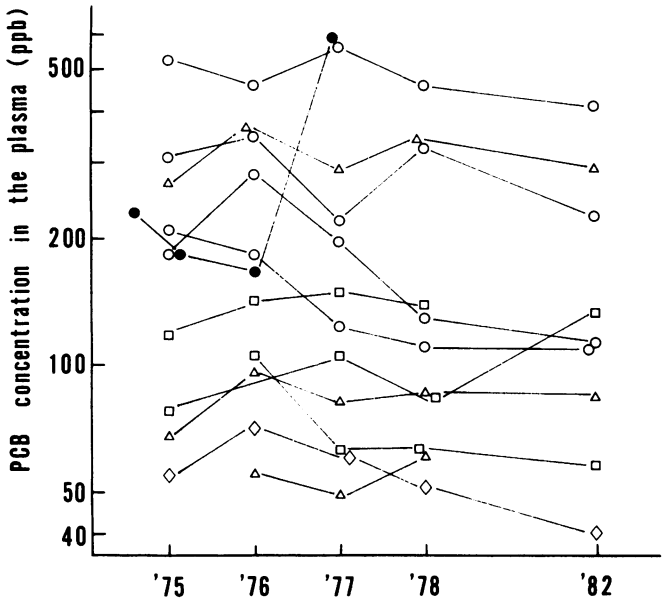

FIGURE 5. Change with time in PCB levels in group A. Subjects with the same mark were working in the same workplace. The subject indicated by solid circles is the first person of group A who was found by chance to have a high level of PCBs.

suggest that the PCB patterns of groups A and C reflect the respective kinds of PCBs to which they were exposed.

Follow-up Study of Blood PCB Levels of Groups A, C and D

Figure 5 shows the temporal change of PCB levels of some subjects with high PCB levels in group A. There was no clear temporal decrease except in some subjects. The change in one subject shown by the solid circles was quite different from that of the others.

Figure 6 shows significant decreases in the PCB levels of group C ($p < 0.01$).

The change of the PCB levels of a certain family in group D with time is described in Figure 7. The solid and open circles show the PCB levels of children who were 6 and 10 years old, respectively, in 1973. They showed a remarkable decrease in PCB level, probably related to their growth, while the adults showed no such tendency. This phenomenon is considered the so-called "dilution effect" of PCBs (*12*).

Change of PCB Patterns of Groups A, C and D with Time

The change with time of the PCB pattern of the four subjects described (open circles) in Figure 5, is shown in Figure 8. This figure reveals a tendency for the component ratio of peak 15 to decrease and for that of peaks 16 and 20 to increase. A significant decrease of the ratio of peak 16 was noticed between 1976 and 1982 ($p < 0.005$). To clarify this tendency, the change with time in the 12

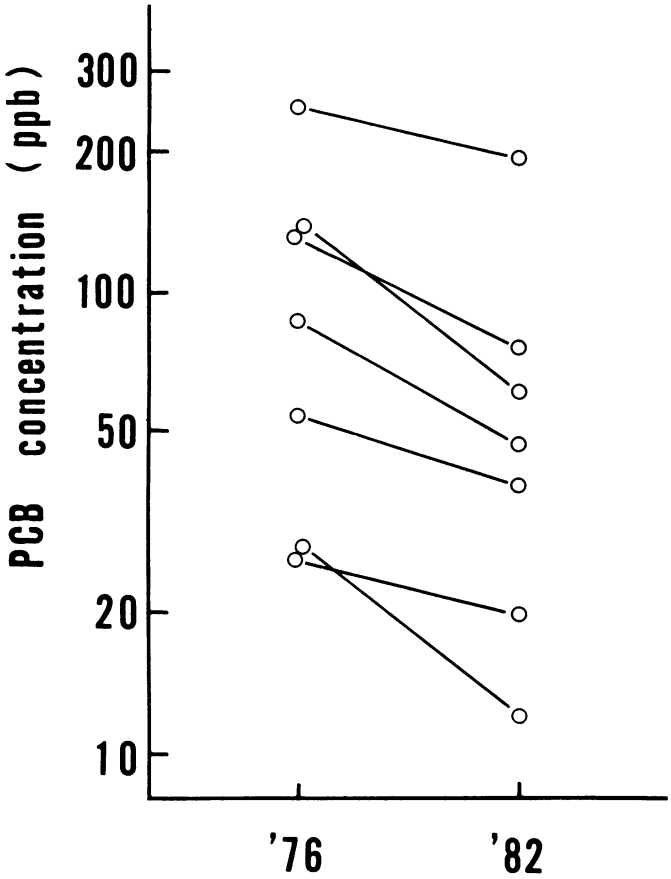

FIGURE 6. Change with time in PCB levels of group C.

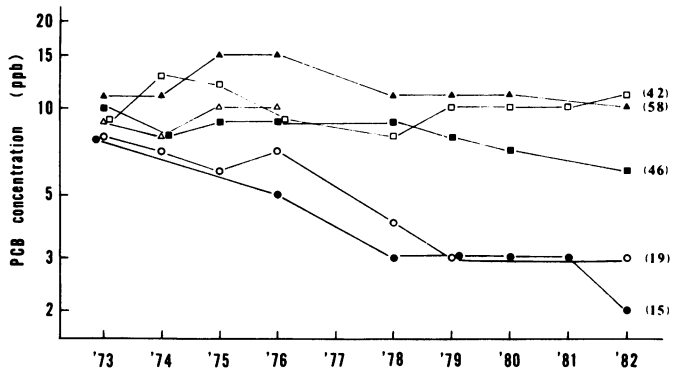

FIGURE 7. Change with time in PCB levels of a family in group D. (The data obtained in the plasma base in 1973–1976 were converted into the whole blood base.)

subjects who were examined in 1978 and 1982 was tested, and a significant decrease of the ratio of peak 15 and significant increases of the ratio of peaks 19, 20, 21 and 22 were noticed ($p < 0.01$).

Figure 9 also shows the change with time of the PCB pattern of the seven subjects in group C. Significant change was noticed at peaks 18, 21, 22 and 23 ($p < 0.05$).

As for Yusho patients, five subjects (Fig. 7) were tested. As shown in Figure 10, the type of change with time was somewhat different from that of groups A and C.

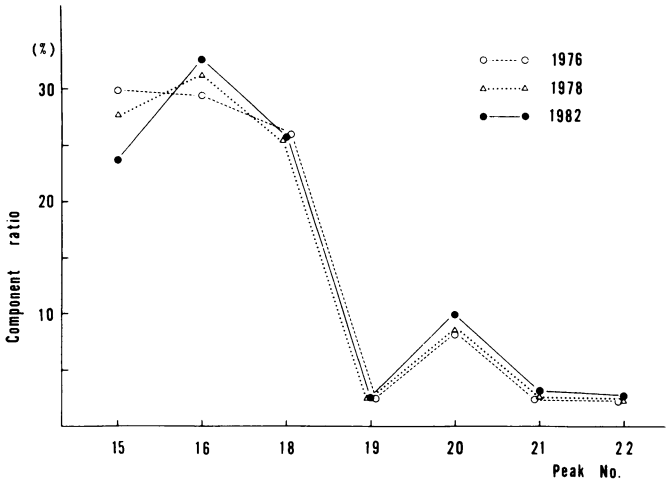

FIGURE 8. Change with time in PCB pattern of mean for four subjects in group A.

Results of Medical Examinations

Group A. Nineteen subjects were examined in 1977. Subjective complaints were within the normal range. Clinical findings included a few acneform eruptions in five subjects, two of them being adolescents.

Triglyceride values in about 50% of the examined subjects exceeded the normal range, without significant correlation between the values and the blood PCB levels. Total cholesterol values were within the normal range. Hepatic function was normal.

Clinical examinations in 1982 showed almost the same results.

Group C. Seven subjects were examined in 1976. There were no subjective complaints except for one subject with a PCB level of 28 ppb who had whole-body fatigue, heavy-headedness, paresthesia and joint pain in the limbs, abdominal pain and so forth. Clinical findings in this subject included acneform eruptions over the face, neck, breast and back, oral mucous pigmentation and excessive palmar sweating. A few other subjects had gingival pigmentation or excessive palmar sweating.

Triglyceride values in the subject with the highest PCB level (252 ppb) exceeded the normal range, showing a high level of β-lipoprotein. Total cholesterol values were within the normal range. Hepatic function was normal.

A significant correlation between blood PCB levels and the triglyceride, total cholesterol, or β-lipoprotein was noticed ($p < 0.05$). Clinical examinations in 1982 showed almost the same results. The subject who had various subjective complaints and clinical findings was suffering from organic solvent intoxication (*13*).

Group D. Members of one family were examined in 1979. Data from periodic health examinations of the family (Fig. 7), 11 years after the outbreak of Yusho episode, are as follows. Subjective complaints included various symptoms, such as abdominal pain, whole-body fatigue and headache among the adults but were absent in the children.

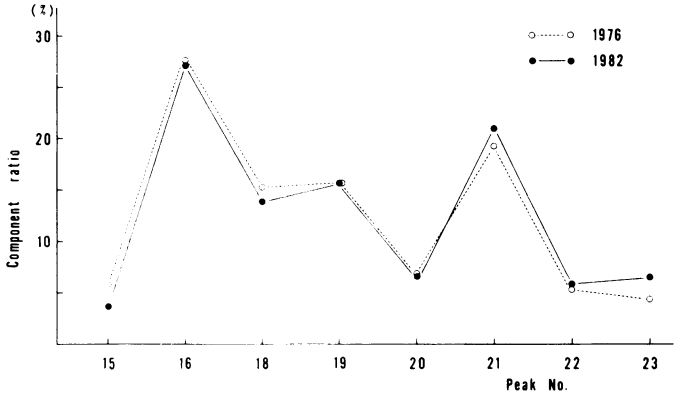

FIGURE 9. Change with time in PCB pattern of mean of group C.

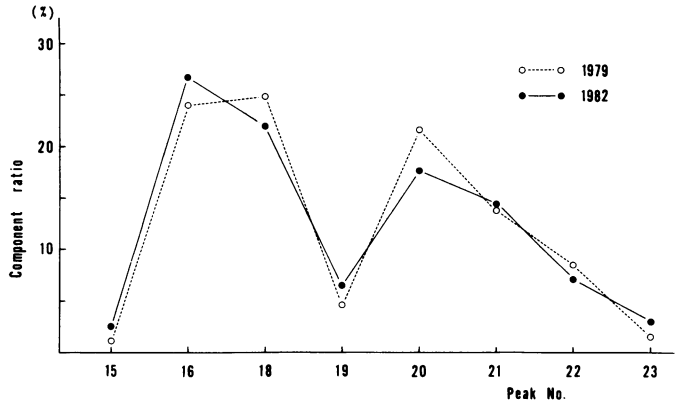

FIGURE 10. Change with time in PCB pattern of mean of five subjects in group D.

The adults had some of the following clinical findings: black comedo, acneform skin eruption, skin pigmentation, pigmentation of the mucous, nail pigmentation, increased eye discharge. The children had mucosal pigmentation and increased eye discharge.

Triglyceride values were within the normal range. Hepatic function was normal. Total cholesterol values were within the normal range.

To summarize, the clinical findings of groups A and C exposed to PCBs of industrial origin were not the same as those of typical Yusho patients, though the PCB levels are suspected to be related to the levels of triglyceride.

PCQ and PCDF Levels

As shown in Table 1, PCQ levels in the plasma of 14 subjects of group A and all of group C were almost the same as in the normal population (lower than the detection limit of 0.02 ppb), though PCB levels were high (6–403 ppb). On the other hand, all the subjects of the family described in Figure 7 (group D) showed PCQ levels of 0.34–5.7 ppb in the whole blood though PCB levels were low (2.0–11.0 ppb).

In the Taiwanese patients (group E), PCDFs as well as PCQs were detected.

Table 1. PCB, PCQ and PCDF levels in the blood of Yusho patients, workers occupationally exposed to PCBs and controls.

Subjects	Group	N	Period after termination of exposure, yr	PCB level, ppb		PCQ level, ppb		PCDF level, ppb	
				Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
Yusho patients (Japan)	D	5	14	2.0–11.0	6.3 ± 4.1	0.34–5.7	2.7 ± 2.2	—	—
Yusho patients (Taiwan)	E	3	1	48.0–78.0	62.6 ± 15.0	10.2–11.8	10.8 ± 0.89	0.062–0.129	0.095 ± 0.034
		5	1.5–2	26.0–71.8	55.4 ± 18.7	4.5–7.8	5.6 ± 1.4	—	—
Workers and their families	A	14	Not clear	6–403	111.5 ± 117.3	< 0.02	—	—	—
Workers	C	7	10	12–196	64.3 ± 62.2	< 0.02	—	—	—
Control	G	40		1.3–5.8	3.4 ± 1.1	< 0.02	—	—	—

Discussion

The latest studies on Yusho have revealed that the rice oil involved was contaminated with PCQs and highly toxic PCDFs (*14–16*). PCDFs were detected in tissues of Japanese Yusho patients (*17*), and Kashimoto et al. (*18*) detected them in the blood of "fresh" Taiwanese patients though they could not be detected in "old" Japanese Yusho patients. From the results of animal experiments, Hori et al. (*19,20*) concluded that PCDFs had played an important role in the manifestation of Yusho findings.

Testing for PCQs in the blood is an important means of determining whether a subject has been exposed to Yusho-type chlorinated hydrocarbons (i.e., PCBs, PCQs and PCDFs) or only to PCBs, though the toxicity of PCQs themselves is almost equal to that of PCBs (*18*). In view of these reports, groups A and C can be judged to have been exposed only to PCBs, because PCQ levels were lower than the detection limit of 0.02 ppb in the two groups. All but one of the subjects in the two groups did not show the clinical findings of Yusho, in spite of their high PCB levels. From these results, we can conclude that the toxicity of PCBs alone is not severe compared with that of Yusho-type chlorinated hydrocarbons.

The same type of PCB contamination as in group A was proven to extend to the cities of Kanazawa and Ichinomiya by the observations of group B. We should pay much attention to the fact that PCB contamination might be hidden because of the lack of information about the existence of PCBs in workplaces.

Because we examined group D more than 10 years after the Yusho episode and consequently the PCB level in these patients had already decreased, a decrease in PCB level with time was not noticed in the adults, only in the children. In the adults belonging to groups A and C, the decrease in PCB level with time was clearer than that of the adults in group D, probably because PCB levels of the former were higher than those of the latter.

As for the change with time of PCB patterns in the workers, the results are considered to agree closely with the report of Watanabe et al. (*21*), i.e., there is a tendency for the relative percentage of highly chlorinated biphenyls to increase with time. In Yusho patients, the change was different from that of the workers. Some factors are considered to contribute to the differences, e.g., metabolic changes relevant to the history of high contamination with Yusho-type chlorinated hydrocarbons, and the effect of food origin PCBs are dominant because their PCB levels are lower than those of the workers.

Conclusions

Some of the workers who were occupationally exposed to KC-500 or KC-600 showed higher PCB levels in the plasma than typical Japanese Yusho patients. Their PCB levels tend to decrease with time.

Gas chromatographic patterns of their PCBs were shown to correspond to the patterns of the PCBs to which they were exposed. The pattern is changing.

PCQ levels in their blood were lower than the detection limit of 0.02 ppb, though PCQs were detected in the blood of typical Yusho patients.

Medical findings or complaints of the workers were slight compared with those of typical Yusho patients.

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