Clinical Pictures of Occupational PCB Poisoning and Yusho/Yu-Cheng Cases: Are They the Same?

Masayuki Ikeda

Department of Public Health, Kyoto University Faculty of Medicine, Kyoto 606-01, Japan

1. Introduction

Polychlorinated biphenyls (PCBs) are well-known toxic chemicals found in the workplaces and in the environment. Due to their unique physico-chemical properties, PCBs had been used in many industries throughout the world, but are presently banned in many but not all countries.

Two large-scale episodes of food poisoning due to PCB contamination occured, one in northern Kyushu Island in Japan in 1968 (Yusho) and the other in Tai-Chung in the central Taiwan in 1979 (Yu-Cheng). Both poisoning cases involved contamination of cooking oil with PCBs. The exposures were different from occupational PCB exposures because pyrolytic products of PCBs such as polychlorinated dibenzofurans (PCDFs) were also found in the contaminated rice oil whereas they are not usually found in PCBs used in the workplaces, as to be discussed later.

The purpose of the present review is to compare clinical symptoms and signs between the two food poisoning cases and occupational poisoning cases in relation to causative chemical agent(s) in the poisoning. Developmental toxicity of Yusho[1,2] and Yu-Cheng[3] oil as well as carcinogenicity potential of PCBs[4] will not be discussed in the present review.

2. Symptoms and signs of Yusho and Yu-Cheng cases

The major clinical findings of the Yusho and Yu-Cheng patients are shown in Table 1. Although the two episodes took place in different populations with a gap in time of more than 10 years, the core clinical picture of the patients is reported to be very similar to each other [5,6]. The typical signs were of oculo-dermal ones, such as swelling of eyelids, increased excretion of Meibomian glands in the eyelids, eruptions (typically chloracne, but also other comedo- and acneform eruptions) and pigmentation of skin of not only face and neck but cloth-protected parts of body. Liver function tests revealed elevated level of serum triglyceride[5], but changes in other liver dysfunction parameters were usually not remarkable. Some patients had numbness of extremities, and sensory neuropathy was detected by electro-physiological examination. Gaschromatographic analysis of blood, liver and adipose tissues proved the presence of PCBs at an increased

Table 1. Symptoms and signs of Yusho and Yu-Cheng patients

Symptoms and signs[5]
Time of episode: Yusho, 1968[7]; Yu-Cheng, 1979[8].
Number of patients: Yusho, 1866 (by 1992)[9]; Yu-Cheng, 2061 (in 3.5 years)[8].
Estimated intake of PCBs/patient: Yusho, 2 g on average (0.5 g as minimum) KC 400[7]; Yu-Cheng, 0.8 to 1.8 g[8] KC 400–KC 500 mixture.
Subjective symptoms:
Loss of appetite, nausea, skin itching, numbness of extremities and feet paresthesia (sensory-dominant neuropathy[10]), joint pain, intractable headache.
Ocular signs:
Eyelids swelling, Meibomian gland hypersecretion, pigmentation and hypertension of conjunctiva, temporary failing of eyesight.
Dermatological signs:
Chloracne, comedo- and acnelike eruption, pigmentation of skin, conjunctiva and nail, excess sweating in palms.
Other findings:
Occasional slight fever, occasional abnormal liver function tests, pulmonary disorder, no obvious anemia, hepatomegaly or splenomegaly.
GC for PCB[8]; specific pattern in chromatogram, increased PCB level.

Modified from Okumura 1984[5]. By 1981, acneform skin eruption, skin and conjunctiva pigmentation, hypersecretion of Meibomian glands, abnormalities in level and chemical nature of PCBs and PCQs in blood were considered as core signs[5]. Clinical pictures of Yu-Cheng were similar to those of Yusho[6].

level, and then of other specific compounds such as PCQs and PCDFs as to be discussed later.

Quantitative estimation made it clear that the average amount of PCBs (KC 400) ingested by Yusho patients was 2 g and the minimum intoxication dose may be 0.5 g[6]; the minimum toxic dose was first estimated to be of 70 μ/kg body weight/day but re-estimated as 35 μg/kg/day or less[11]. In Yu-Cheng cases, the estimated average ingested dose of PCBs (a mixture of KC 400 and KC 500) was 0.8 to 1.8 g[8], being essentially the same with the Yusho cases; although PCB levels in Yu-Cheng rice oil were about 1/10 of that in Yusho rice oil, Yu-Cheng patients consumed much more oil than Yusho patients[12].

3. Levels of PCBs in the blood of Yusho and Yu-Cheng patients

The gaschromatographic methods to measure PCBs in biological specimens became available around 1972. Soon, it was found that the blood samples from Yusho patients, especially with the typical clinical picture, had a specific pattern (so-called 'Pattern A') in the chromatogram. Chronolagical results of blood analysis for PCB ane shown in Table 2. In the cases of Yu-Cheng, the GC method was applicable soon after the outbreak. The analyses showed that the mode of PCB levels in blood was in the range of 51 to 100 μg/l serum, although the whole sample values distributed in a quite wide

range. The PCB levels in the blood of Yusho patients at the time of the outbreak was not known. The chronological analysis appears to suggest that PCBs in blood have been at the levels around 7 μg/l and disappearing only slowly (i.e., with a long biological half-time).

Recently, Masuda and his co-workers[20] examined elimination of PCBs and PCDFs from the blood of Yu-Cheng patients and found that the biological half-time is 2.1 years for 2,4,3',4'-tetra-CB, 1.2 years for 2,4,5,3',4'-penta-CB, and 4.1 to 4.6 years for two each of hexa- and hepta-CBs, whereas it is 2.1 to 2.5 years for three penta- to hepta-CDFs. In an accidental exposure to PCBs in a capacitor production plant, Elo et al.[21] observed thet the PCB levels in serum returned to below the reference limit level in a month or so, probably reflecting the rapid phase of PCB disapperance. Kitamura et al.[22] obtained an estimate of a PCB half-time of 90 days in their observation on the capacitor workers after termination of exposure. Wolff et al.[23] found in a similar study that the velocity of disapperance of PCBs from the serum varies depending on the PCB congeners and estimated that the half-time would be 8.6 years for lower PCBs (i.e., mono- to tetra-CBs) and 65 years for higher PCBs (i.e., penta- to octa-CBs). As Yusho rice oil was contaminated with KC 400 (the major component being tetra-CBs), the half-time estimates by Wolff et al.[19] will lead to an assumption that the PCB levels in the serum of Yusho patients at the time of the outbreak may not differ very much from the levels reported for Yu-Cheng patients.

4. Clinical pictures among PCB-exposed factory workers

There are at least 15 occupational health studies [22,24-37] in which both health status of workers and PCB levels in their blood were examined. The major findings in these reports are summarized in Table 3. Hasegawa[29] estimated that the PCB intake of PCB-exposed workers via inhalation would be 1.2 mg/day. It was also noticed that skin of

Table 2. PCB levels in the serum/plasma of Yusho and Yu-Cheng patients

Case Time[a]	Levels[b] (μg/l)	Ref.	Case Time[a]	Levels[b] (μg/l)	Ref.
Yusho[c]			1977	7.0 (92)[d]	16
1972	6.3±4.0 (15)	13	1977	11.1±11.6 (23)	17
1973	6.7±5.3 (41)	12	1988	4.8±3.5 [0.6–32] (259)	18
1973–4	5.9±4.5 (72)	15	1989	6.4±3.2 (27)	19
1974	8.7 (127)[d]	16	Yu-Cheng		
1976	8.5 (79)[d]	16	1 year[e]	3–1156 (mode 51–100)	8

a/ The year of blood sampling.
b/ Either mean±SD or the range (number of subjects in parentheses).
c/ Methods of GC analyses for PCBs were not available till 1972.
d/ Patients with Pattern A Chromatograms.
e/ Pooled data with blood samples collected within 1 year after the outbreak.

the workers were often contaminated with liquid PCBs and the absorption of PCBs through intact skin should be an important route of body entry[38,39]. Accordingly, PCB levels are taken as an indicator of intensity of exposure to PCBs. It should be noted that the blood samples were taken in these studies while the workers were still exposed or shortly after the termination of exposure due to no further PCB use in plants.

The arrangement of the occupationally exposed groups in increasing order of serum/plasma PCB levels is shown in Table 3, although it might not be appropriate to make simple comparison because some authors expressed the PCB levels in terms of geometric means or medians whereas others in arithmetic means or in ranges. Many of the PCB-exposed workers had PCB levels higher than those of the Yusho and Yu-Cheng patients. In contrast, the clinical picture of the PCB-exposed workers was much milder than that of the patients of the two episodes, although most of the occupational health

Table 3. Clinical pictures of workers occupationally exposed to PCBs

PCBs-S/P[a]	Signs[b]				Remarks	Ref.
	A.	P.	L.	H.		
ND–300	+[c]				No other clinical signs	24
2–251	+	+	+?		Less intense than Yusho patients	25
10–312			+		Increase in AST & ALT, but none else	26
12.2[d]					Essentially no abnormalities	27
18.2[d] (0–424)	–	–	–		No pathological changes in liver and skin	28
20–920	+?	+?	–		No disorder in lipid metabolism	29
20–2100	+	–	–	–	Biological half-time; ca. 90 days	22
41–1319	+		+		No correlation of signs with PCB-S level	30
63 (18)[e]					Paucity of eye/skin findings	31
117 or less	+				Signs mostly dermatological	32
124 (48)[f]	+	+	–	–	Paucity of abnormalities in physical exam.	33
400[g]	+		–		Abnormal sense in face and hands	34
2270 (142)[h]					No clinical signs except for elevated Tg[i]	35
3330 (250)[h]			+?		Reduced sense, increase in Tg[i]	36
??					Skin abnormalities in 37% of the exposed	37

a/ Unit; μg/l. Unless otherwise specified, values show ranges.
b/ A., Acne (including chloracne); P., pigmentation of skin, conjunctiva or nail; L., liver dysfunction; H., abnormal hematology.
c/ Comedones. No chloracne.
d/ Geometric mean.
e/ Median lower PCBs (median higher PCBs): Lower and higher PCBs mean mono- to tetra-CBs and penta- to octa-CBs, respectively.
f/ Mean of lower PCBs (mean of higher PCBs).
g/ Probably arithmetic mean.
h/ The maximum of lower PCBs (the maximum of higher PCBs).
i/ Triglyceride in serum.

studies were conducted with knowledge about the clinical findings of the Yusho and Yu-Cheng patients. For example, Acquavella et al.[28] reported that the physician in charge did not detect liver or skin abnormalities that might be attributable to PCB exposures for any of their study subjects who had 0 to 424 μg/l PCBs in their blood. Similarly, Emmett et al.[24] summarized their observation on workers (serum PCBs; ND to 300 μg/l) that no subjects had a classic syndrome of PCB poisoning and no evidence of classic chloracne was noted, although comedones were more frequent in the exposed group. Smith et al.[36] examined more than 400 PCB-exposed workers in various factories (for PCBs in serum, see Table 3) and concluded that no consistent patterns of abnormalities were noted and that no worker had acneform skin lesions suggestive of chloracne. Such striking paucity of abnormal findings in physical examination has been noticed by some of the occupational health scientists (e.g., Ref. 29). In this respect, the study of Takamatsu and others[25] should be worthy of citation because they were among very few who could examine both Yusho patients and PCB-exposed factory workers. In their opinion, clinical findings and subjective complaints of 7 PCB workers (PCBs in plasma: 12–196 μg/l) were usually slight compared with 23 typical Yusho patients (PCBs in plasma: 2–11 μg/l), although some of the workers had slight dermal manifestations (one case of acneform skin eruption and a few cases of pigmentation and excessive palmar sweating) and their serum triglyceride levels seemed to be related to serum PCB levels.

5. Possible causative agents of Yusho and Yu-Cheng disease

This review of the existing reports on Yusho, Yu-Cheng and cases of occupational exposure to PCBs has made it clear that dose-response relationship is different between the two food poisoning cases and occupational PCB poisoning, in agreement with the suspicion of Masuda and Kuratsune[11] that causative agent(s) other than PCBs (e.g., PCDFs and PCQs) might be involved in the former two cases. In fact it was confirmed that both PCDFs and PCQs in addition to PCBs were present in Yusho rice oil and Yu-Cheng rice oil[12], as well as biological specimens from the patients[40,41], and that heating of PCBs will result in formation of these impurities under experimental conditions[42,43]. Furthermore, Kunita and others[44] extracted PCBs (PY-PCBs), PCDFs (PY-PCDFs) and PCQs (PY-PCQs) from Yusho rice oil and administered them to monkeys. The monkeys (ca. 2.5 kg in body weight) given PY-PCDFs (20 μg/head/day) (but not those given PY-PCBs or PY-PCQs) developed Yusho-like signs such as edema of eyelids, acneform eruption, and pigmentation in cheek and nose, indicating that PCDFs are the chemicals causative of dermatological signs in Yusho disease. 2,3,4,7,8-Penta-CDF has been suspected to be the most important etiologic agent[12]. PCDF concentration in Yusho rice oil was estimated to be almost 300 times higher than the levels calculated from PCDF concentration in fresh KC 400[45].

6. References (* in Japanese with English abstract; † in Japanese)

1) Yoshimura, T. (1971) Fukuoka Acta Med., 62, 109–116*
2) Yamaguchi, A., et al. (1971) Fukuoka Acta Med., 62, 117–122*
3) Yu, M.-L., et al. (1991) Neurotoxicol. Teratol. 13, 195–202

4) Yassi, A., et al. (1994) Am. J. Ind. Med. 25, 425–437
5) Okumura, M. (1984) Am. J. Ind. Med. 5, 13–18
6) Lü, Y.-C., and Wong, P.-N. (1984) Am. J. Ind. Med. 5, 81–115
7) Kuratsune, M. et al. (1972) Environ. Health Perspect. 1, 119–128
8) Hsu, S.-T., et al. (1985) Environ. Health Perspect. 59, 5–10
9) Asahi, M. (1993) J Univ. Occup. Environ. Health 15, 1–11*
10) Murai, Y., and Kuroiwa, Y. (1971) Neurology 21, 1173–1176
11) Masuda, Y., and Kuratsune, M. (1979)Fukuoka Acta Med. 70, 229–237
12) Masuda, Y., et al. (1982) Chemosphere 11, 199–206
13) Takamatsu, M. et al. (1974) Fukuoka Acta Med. 65, 28–31*
14) Masuda, Y., et al. (1974) Fukuoka Acta Med. 65, 25–27
15) Koda, H., and Masuda, Y. (1975) Fukuoka Acta Med. 66, 624–628*
16) Okumura, M., et al. (1979) Fukuoka Acta Med. 70, 199–207*
17) Takamatsu, M., et al. (1979) Fukuoka Acta Med. 70, 223–228*
18) Hirota, Y., et al. (1991) Fukuoka Acta Med. 82, 335–341*
19) Ohgami, T., et al. (1991) Fukuoka Acta Med. 82, 295–299*
20) Masuda, Y., et al. (1991) Fukuoka Acta Med. 82, 262–268*
21) Elo, O., et al. (1985) Environ. Health Perspect. 60, 315–319
22) Kitamura, S., et al. (1973) 46th Meet. Jpn. Assoc. Ind. Health, Abst. No. 441
23) Wolff, M. S., et al. (1992) Environ. Res. 59, 202–216
24) Emmett, E., et al. (1988) Am. J. Ind. Med. 13, 415–427
25) Takamatsu, M., et al. (1985) Environ. Health Perspect. 59, 91–97
26) Chase, K. H., et al. (1982) J. Occup. Med. 24, 109–114
27) Emmett, E. A. (1985) Environ. Health Perspect. 60, 185–192
28) Acquavella, J. F., et al. (1986) J. Occup. Med. 28, 1177–1180
29) Hasegawa, H., et al. (1972) Occup. Health (Rodo Eisei) 13(10), 55–55†
30) Maroni, M., et al. (1981) Br. J. Ind. Med., 38, 55–60
31) Fischbein, A., et al. (1985) Br. J. Ind. Med. 42, 426–430
32) Hara, I. (1985) Environ. Health Perspect. 59, 85–90
33) Fischbein, A., et al. (1979) Annn. N.Y. Acad. Sci. 320, 703–715
34) Ouw, H. K., et al. (1976) Arch. Environ. Health 31, 189–194
35) Lawton, R. W., et al. (1985) Environ. Health Perspect. 60, 165–184
36) Smith, A. B., et al. (1982) Br. J. Ind. Med. 39, 361–369
37) Fischbein, A., et al. (1982) Arch. Environ. Health 37, 90–74
38) Maroni, M., et al. (1981) Br. J. Ind. Med. 38, 49–54
39) Lees, et al. (1987) Am. Ind. Hyg. Assoc. J. 48, 257–264
40) Rappe, K., and Buser, H. R. (1979) Chemosphere 8, 259–266
41) Kashimoto, T., et al. (1985) Environ. Health Perspect. 59, 73–78
42) Morita, M. (1977) IUPAC Meeting, p. 361,.Tokyo
43) Buser, H. R., et al. (1978) Chemosphere 7, 109–119
44) Kunita, N., et al. (1984) Am. J. Ind. Med. 5, 45–58
45) Masuda, Y., and Yoshimura, H. (1984) Am. J. Ind. Med. 5, 31–44