Environmental Health Perspectives
Vol. 59, pp. 79-84, 1985

Biological Effect of PCBs, PCQs and PCDFs Present in the Oil Causing Yusho and Yu-Cheng

by Nobuharu Kunita,* Shinjiro Hori,* Hirotaka Obana,* Toru Otake,* Hiroshi Nishimura,* Takashi Kashimoto* and Nobuko Ikegami†

Male Sprague-Dawley rats were daily given orally for 22 days a regimen consisting of polychlorinated biphenyls (PCBs), 1 mg/day; polychlorinated quaterphenyls (PCQs), 1 mg/day; polychlorinated dibenzofurans (PCDFs), 10 μg/day; or a mixture of PCBs, PCQs and PCDFs (Mix-1, 1 mg + 1 mg + 10 μg/day).

Female Cynomolgus monkeys were daily administered PCBs (5 mg), PCQs (5 mg) or a mixture (Mix-2) containing 5 mg PCBs + 20 μg PCDFs for 20 weeks. The PCBs, and PCDFs had the components of PCBs, PCQs and PCDFs similar to those contained in Japanese Yusho oils, respectively.

The PCB-treated rats and monkeys showed hepatic hypertrophy, immunosuppression and increased drug-metabolizing enzyme activities in hepatic microsomes, but were devoid of the dermal symptoms characteristic of Yusho. PCQs caused an increase in drug-metabolizing enzyme activities in hepatic microsomes and immunosuppression in monkeys, but these effects were much smaller than those found with PCBs treatment.

On the other hand, treatment with PCDF or Mix-1 or Mix-2 caused hypertrophy of the liver, immunosuppression, increase in drug-metabolizing enzyme activities of hepatic microsome to much greater extent than observed with PCBs, being more than 100 times as effective as PCBs. In addition PCDFs and the mixtures containing PCDFs caused weight loss and thymic atrophy.

PCDFs and Mix-2-treated monkeys showed the dermal symptoms that are characteristic of Yusho patients but were not observed in monkeys treated with PCBs and PCQs alone. These results suggest that PCDFs are the primary causative agent of Yusho.

Introduction

Yusho is a complicated polychlorinated biphenyl (PCB) poisoning (*1*), since PCBs, which have been regarded as the principal causative substance of this poisoning, are composed of a number of isomers of different nature, and since the toxic rice oil causing Yusho contains, in addition, polychlorinated quaterphenyls (PCQs) (*2*) and highly toxic polychlorinated dibenzofurans (PCDFs) (*3*). Recently, it has been found that PCB isomers vary greatly in toxicity (*4–6*). Moreover, PCQs (*7*) and PCDFs (*8*) have been detected in samples of blood and some organs of patients with Yusho.

Therefore, to understand the nature of the chemical substances responsible for Yusho, PCB, PCQ and PCDF samples resembling in composition the PCBs, PCQs and PCDFs found in the toxic rice oil were prepared in our laboratory by distilling KC-400 under reduced pressure. The present paper reports an experimental study of the toxicity of these PCBs, PCQs and PCDFs to rats and monkeys and presents a possible interpretation of human intoxication by the polychlorinated compounds.

Experimental

Rats

Male Sprague-Dawley rats (5 weeks old, weighing about 150 g) were raised in stainless-steel cages without bedding in an air-conditioned room with water and rat chow (Oriental Yeast Co. Ltd., Japan) *ad libitum*.

†National Osaka Hospital, 1, Hoenzaka, Higashi-Ku, Osaka 540, Japan.
*Osaka Prefectural Institute of Public Health, 1-3-69, Nakamich, Higashinari-Ku, Osaka 537, Japan.

For oral administration, the PCBs, PCQs, PCDFs or Mix-1 were dissolved in olive oil. The daily dose of each sample of PCBs, PCQs, PCDFs or mix is listed in Table 1. All rats were observed daily for evidence of changes in demeanor and appearance. Body weights were recorded daily during treatment and thereafter. Each group was divided into five subgroups of six each and sacrificed at 5, 10 and 22 days of treatment and 10 and 24 days after cessation of treatment.

Monkeys

Ten female Cynomolugus monkeys (*Macaca fascicularis*) weighing approximately 2.5 kg were obtained from Malaya, and reared for 3 months in individual cages in air-conditioned rooms before starting experiments. During the 20-week experimental period, monkeys were daily fed bread (30 g), monkey chow (100 g, Oriental Yeast Co., Japan) and bananas (50 g), and were given water *ad libitum*.

For oral administration, the PCBs, PCQs, PCDFs and Mix-2 were dissolved in olive oil, and the daily dose (Table 1) was injected into a piece of banana (50 g) given to the monkeys once a day, except Sundays, for 20 weeks.

The monkeys were observed daily for physical and clinical signs, and were weighed and bled at 4-week intervals throughout the experimental feeding period. Finally they were examined by autopsy for pathologic changes in their internal organs. The monkeys fed PCDFs (Nos. 4, 5 and 6) were killed in week 16, because they appeared to be close to death.

Chemicals

KC-400 and PY-PCQs were obtained from Kanegafuchi Chemical Ind. Co. (Kyogo, Japan).

PY-PCBs and PY-PCDFs were prepared from a KC-400 as described in Table 1 and the previous report (*9*).

PY-PCBs, PY-PCQs and PY-PCDFs had composition of PCBs, PCQs and PCDFs similar to those contained in the Japanese toxic rice oils. Mixture 1 (abbreviated Mix-1) was a complex mixture of PY-PCBs, PY-PCQs and PY-PCDFs in proportions of 1:1:0.01 (the approximate proportion of these compounds in toxic rice oil), and Mixtures 2 (abbreviated Mix-2) was a complex of PY-PCBs and PY-PCDFs, 1:0.0004.

Immunization and Assay for Anti-Sheep Red Blood Cell (SRBC) Antibodies

All rats or monkeys were immunized three times with 0.5 mL and 1.5 mL of 10% SRBC in physiological saline. Blood samples were collected 12 days after each immunication. Serum samples were stored at – 20°C until assayed for anti-SRBC antibody and immunoglobulin (IgG) levels.

The hemolysin titer was measured by 100% hemolysis method (*10*). The quantitation of IgG was carried out according to the method described by Otake et al. (*11*).

Enzyme Assays

Microsomal protein concentration was measured according to the method of Lowry et al. (*12*). Cytochrome P-450 content was determined by the method of Omura and Sato (*13*). Microsomal *N*-demethylation of aminopyrine and *O*-demethylation of *p*-nitroanisole and NADPH-cytochrome c reductase were quantified by the method described the previous report (14). Benzo(a)pyrene hydroxylase activity was measured by the method of Nebert and Gelboin (*15*).

Table 1. Experimental groups.

Animal	Compounds	Daily dose fed per animal	Feeding periods
Rats[a]	PY-PCBs[b]	1 mg	22 days
	PY-PCQs[c]	1 mg	22 days
	PY-PCDFs[d]	10 μg	22 days
	Mix-1 (PY-PCBs + PY-PCQs + PY-PCDFs)[e]	1 mg + 1 mg + 10 μg	22 days
	None (control)	—	22 days
Monkeys[f]			
No. 1	PY-PCBs	5 mg	20 weeks
Nos. 2,3	PY-PCQs	5 mg	20 weeks
Nos. 4,5,6	PY-PCDFs	20 μg	16 weeks[g]
Nos. 7	Mix-2[h]	5 mg	20 weeks
Nos. 8,9,10	None (control)	—	20 weeks

[a]Male Sprague-Dawley rats (5 weeks old); six rats per group.
[b]PY-PCBs were prepared from KC-400 by distillation under reduced pressure; PCDFs and PCQs were removed by Florisil column chromatography. The composition of PCBs in the PY-PCBs is similar to that of the PCB-contaminated Kanemi rice oil sample which caused Yusho (toxic rice oil).
[c]The composition of PCQ in the PY-PCQs is similar to that of the PCQ-contaminated toxic rice oil.
[d]PY-PCDFs were prepared from KC-400 by distillation under reduced pressure and PCBs and PCQs were removed by Florisil column chromatography. The composition of PCDF in the PY-PCDFs is similar to that of the PCDF-contaminated toxic rice oil.
[e]Mix-1 is similar to the proportions of PCBs, PCQs and PCDFs in the toxic rice oil.
[f]Female Cynomolgus monkeys weighing approximately 2.5 kg.
[g]Monkeys 4, 5, and 6 became moribund and were killed on week 16 of feeding.
[h]Mix-2 is the PY-PCBs with PCDFs of 400 ppm.

Results

Rat

The inhibition of the increase in body weight was noted only in the PY-PCDFs group and Mix-1 group with PY-PCDFs. The tendency continued also following discontinuance of administration.

Changes in the weight ratios of the organs were noted for the liver and the thymus: namely, the ratio for the liver increased in each group except for the PY-PCQs group, especially in the Mix-1 group. On the other hand, marked atrophy of the thymus was noted in the PY-PCDFs group and Mix-1 group. This atrophy was still observed on the day 24 after administration was discontinued.

The PY-PCBs group showed increased alkaline phosphatase (AlP), glutamic oxaloacetic transaminase (GOT) and cholesterol levels. By contrast, the Mix-1 group (a toxic rice oil minic) showed a significant decrease in glutamic pyruvic transaminase (GPT) and a significant increase in cholesterol level. The groups administered PCBs, PCQs and PCDFs showed no significant increase in triglycerides, a value which was reported to increase in Yusho patients, but the Mix-1 group showed a significant increase in that value.

Rats of each group were immunized three times with SBRC and 12 days after each challenge their ability to produce anti-SRBC antibody and blood IgG level was determined. The suppression of the anti-SRBC antibody production was seen on day 22 of administration in the groups of Mix-1, PY-PCBs and PY-PCDFs, among which the Mix-1 group showed the most marked suppression. Blood IgG level and leukocytes also tended to decrease. In addition the suppression was still noted even on day 24 after discontinuance of administration of the toxic oil components. On the contrary, the PY-PCQs group scarcely exhibited suppression of the anti-SRBC antibody production (Fig. 1).

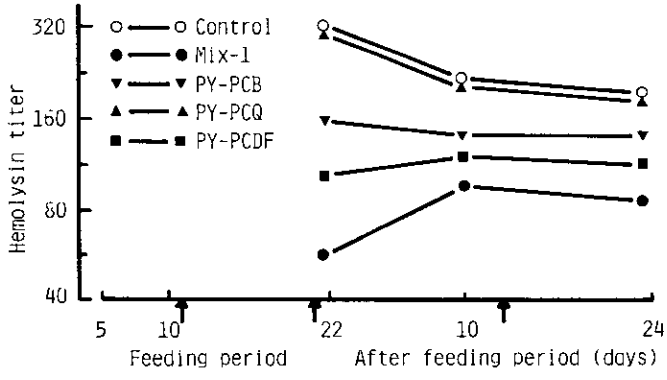

FIGURE 1. Effects of PY-PCBs, PY-PCQs, PY-PCDFs and Mix-1 on hemolysin titer of rats. Rats were immunized three times with 0.5 mL of 10% SRBC in physiological saline and blood samples were collected 12 days after each immunization. PY-PCBs (1 mg/day), PY-PCQs (1 mg/day), PY-PCDFs (10 μg/day) or Mix-1 (PY-PCBs 1 mg + PY-PCQs 1 mg + PY-PCDFs 10 μg/day) were given orally to each rat.

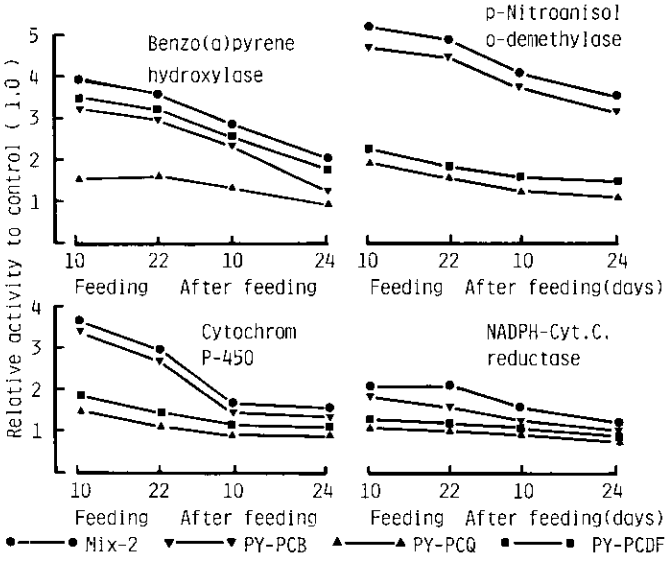

FIGURE 2. Comparative effects of pretreatment with PY-PCBs, PY-PCQs, PY-PCDFs and Mix-1 on liver enzyme activities in rats. PY-PCBs (1 mg/day), PY-PCQs (1 mg/day), PY-PCDFs (10 μg/day) or Mix-1 (PY-PCBs 1 mg + PY-PCQs 1 mg + PY-PCDFs 10 μg/day) were given orally to each rat.

Figure 2 shows the activities of induction of hepatic microsomal drug metabolizing enzymes. PCBs increased the activity of cytochrome P-450, *p*-nitroanisole *O*-demethylase, aminopyrine *N*-demethylase and benzo(a) pyrene hydroxylase. The pattern of the enzyme induction showed a mixture of phenobarbital (PB)- and 3-methylcholanthrene (MC)-types, in good agreement with the observed shift of the absorption maximum to 449 nm in the CO-difference spectra. The enzyme-inducing ability of PCQs was weaker than that of other test substances and showed a mixed-type induction of PB and MC. PCDFs strongly induced benzo(a)pyrene hydroxylase, showing MC-type induction, whereas Mix-1 showed strong inducing effects upon all the enzymes.

The effects of PCQs on rats were far weaker than those of PCBs. PCDFs, however, had intensive effects on rats, despite the fact that the dose was only one-hundredth that of PY-PCBs or PY-PCQs. In other words, the toxicity of PY-PCDFs in rats is 100 times that of PCBs or PCQs. However, even with PCDFs and Mix-1 it was not possible to evoke cutaneous symptoms such as the dermal acneform lesions characteristic of Yusho.

Therefore, we studied the influence of Yusho-related compounds on female monkeys which were assumed to be more susceptible to PCBs than rats and attempted to reproduce Yusho symptoms in these animals.

Monkey

Monkeys treated with Mix-2 and PCDFs showed a decrease in body weight; approximately a 15% decrease in both groups 12 weeks after the beginning of the experiment. The food consumption of these monkeys

during the experimental perod was not different from that of the monkeys fed PCBs, PCQs and control monkeys. The monkeys on PCBs and PCQs kept the initial body weight or had a slight weight gain.

Figure 3 shows the organ weight per unit body weight of monkeys and activities of hepatic drug-metabolizing enzymes. Among the organs tested, liver was the most profoundly influenced by the test substances. The Mix-2-treated monkey showed markedly increased liver weight, about 2.4 times that of control monkeys, and also showed hypertrophy of kidney and spleen. Further, PCDF-treated monkeys showed greater hypertrophy of spleen than was found in other test animals.

As shown in Figure 3, activities of cytochrome P-450, benzo(a)pyrene hydroxylase and aminopyrine *N*-demethylase increased in all the monkeys except PCDF-treated monkeys. In particular, this tendency was the most marked with the Mix-2 animal. In contrast, in monkeys fed PCDFs, the activities of cytochrome P-450, aminopyrine *N*-demethylase, and benzo(a)pyrene hydroxylase were 80, 50 and 50%, respectively, of those of the control monkeys. We consider the observed low enzymatic activities of PCDF-treated monkeys were due to the extreme asthenia of these monkeys at the time of dissection.

On immunological study, Mix-2 and PY-PCB-treated monkeys showed marked suppression of anti-SRBC antibody production, the antibody titer being less than 5 before the second immuization. The monkey fed PCBs (without PCDFs) showed increased antibody production after the second immunization, while administration of Mix-2 (with PCDFs) caused suppression of antibody-producing ability throughout the experimental period (Fig. 4). Further, in contrast to monkeys treated with PY-PCBs, PY-PCDF-treated monkeys showed continuous decrease in antibody production with time, reaching about the same extent of suppression after 16 weeks as that of Mix-2-treated monkey. PCQs were also found to suppress antibody-producing ability (Fig. 4).

Monkeys treated with PY-PCDFs or Mix-2 (with PCDF) showed hair loss, periorbital edema, Meibomian retention cysts, and acneforms lesions on faces—all characteristic symptoms of Yusho disease. Further, these monkeys showed the enlargement of hyperkeratinosis of pilar pores, and the degeneration of hair root on the dorsal skin.

In contrast, the control monkeys and those treated with PY-PCBs or PY-PCQs did not show any of the clinical symptoms characteristic of Yusho as were observed in monkeys treated with PY-PCDFs and Mix-2 (with PCDFs).

Discussion

It is well known that PCBs have a strong inducing effect on the drug-metabolizing enzymes of hepatic

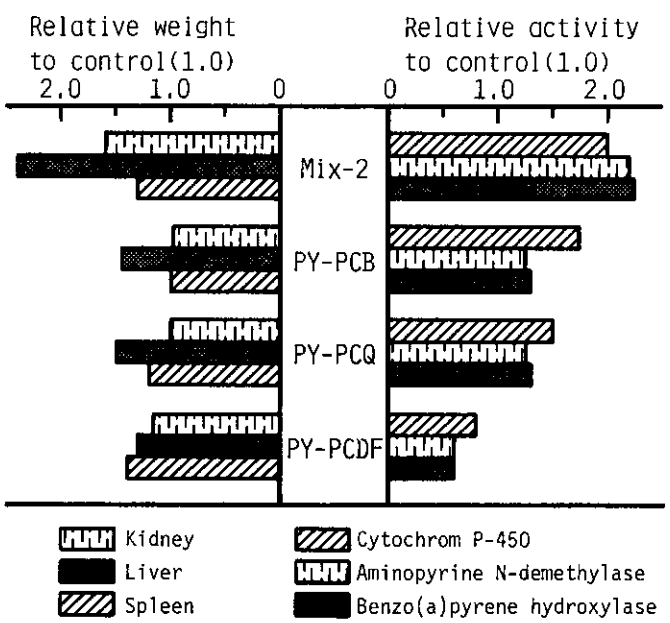

FIGURE 3. Comparative effects of pretreatment with PY-PCBs, POY-PCQs, PY-PCDFs and Mix-2 on liver enzyme activities and organ weights in monkeys. PY-PCBs (5 mg/day), PY-PCQs (5 mg/day) or Mix-2 (5 mg/day) were given orally for 20 weeks. PY-PCDFs (20 μg/day) were given orally for 16 weeks.

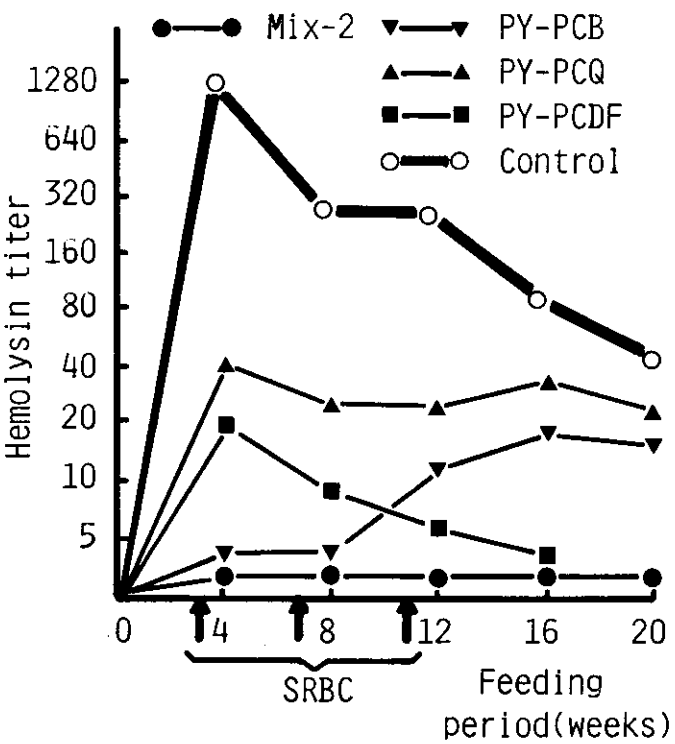

FIGURE 4. Effects of PY-PCBs, PY-PCQs, PY-PCDFs and Mix-2 feeding on anti-SRBC antibody. Monkeys were immunized with 1.5 mL of 10% SRBC in physiological saline on days 16, 44 and 72 of feeding. The blood samples were collected 12 days after each immunization. PY-PCBs (5 mg/day), PY-PCQs (5 mg/day) or Mix-2 (5 mg/day) were given orally for 20 weeks. PY-PCDFs (20 μg/day) were given orally for 16 weeks.

microsomes (*16,17*), and Kanechlor and other PCB products are mixtures of phenobarbital (PB) and 3-methylcholanthrene (MC) type PCBs (*16*). Recently, Yoshimura et al. (*4*) demonstrated that MC-type PCBs exhibited marked toxic effects that PB-type PCBs did not share: hypertrophy of liver and atrophy of thymus. They also clearly showed a positive correlation between the ability of MC-type PCBs to induce activity of liver enzymes and toxicity. The present study revealed that PY-PCBs, which have similar composition to the PCBs in the toxic rice oil, have mixed type inducing ability, as is the case with commercial PCB products. The enzyme-inducing ability of PY-PCBs is stronger than that of KC-400 as judged by our experiments with KC-400 administered to rats (unpublished data) and monkeys (*9,14*). PY-PCQs, which have similar composition to PCQs in the toxic rice oil, also caused enzyme induction of the same type as PY-PCBs, but to a much smaller extent. On the other hand, PY-PCDFs and mixtures containing PCDFs (Mix-1 and Mix-2) caused MC-type enzyme induction and further brought about decrease in body weight and marked atrophy of thymus which were not observed in PY-PCB- or PY-PCQ-treated animals. These results are consistent with the report of Yoshimura et al. (*4*) described above.

Loose et al. (*18*) reported that administration of Aroclor to mice caused a decrease in anti-SRBC antibody-producing ability and serum IgG level. The present study demonstrates the suppression of immune system in PY-PCB-treated rats and monkeys, in agreement with the report of Loose (*18*) and Thomas (*19*). The fact that PY-PCQ-treated monkey showed suppression of anti-SRBC antibody-producing ability that was not observed in similarly treated rats indicates that monkeys are highly susceptible to these organochlorine compounds. Administration to rats and monkeys of PY-PCDFs of composition analogous to that of PCDFs in the toxic rice oil produced more marked immunosuppression than PY-PCBs, in spite of the 100-fold difference in amount administered.

As demonstrated above, PY-PCDFs and Mix-1 exhibited marked effects on rats with respect to body weight increase, immunosuppression, enzyme induction, and blood biochemical finding, but the dermal symptoms characteristic of Yusho patients could not be observed. However, administration of PY-PCDFs and Mix-2 to monkeys made it possible to reproduce Yusho symptoms. Thus, administration of PY-PCBs or PY-PCQs alone to monkeys did not cause Yusho symptoms. These results indicate that PCDFs are the compounds responsible for the developoment of Yusho symptoms.

In our experiments, the calculated doses of PY-PCBs and PY-PCDFs required for the induction of the dermal symptoms in monkey fed Mix-2, as converted to the dose per average human body weight (50 kg), were 600 mg and 2.4 mg. Hayabuchi et al. (*20*) who investigated the biochemical aspects, estimated the critical doses as 466 mg for PCBs, 439 mg for PCQs, and 2.5 mg for PCDFs, which values agree quite well with the data from monkeys. Further, even administration of PY-PCDFs alone caused Yusho symptoms, while administration to monkeys of PY-PCBs or PY-PCQs which contained no PCDFs did not cause Yusho symptoms even at a dose approximately 13 times the dose ingested by Yusho patients.

Hara et al. (*21*) and other investigators (*22*) reported that the clinical symptoms of patients occupationally exposed to PCBs were much milder than those of Yusho patients, and the blood PCB composition of the former patients was clearly different from that of Yusho patients. Further, Yu-Cheng patients of Taiwan show much graver symptoms than the patients occupationally exposed to PCBs, in spite of the fact that the blood PCB level of the former is less than or at most in the same range as that of the latter (*22,23*).

The present study with monkeys clearly indicates that the observed differences between the symptoms of the patients occupationally exposed to PCBs and Yusho patients are due not to a difference in the composition between commercial PCB products and toxic rice oil, but to the presence of PCDFs in the toxic rice oil and suggests that PCDFs are the primary causative agents of Yusho.

REFERENCES

1. Katsuki, S. Foreword. Fukuoka Acta Med. 60: 403–408 (1969).
2. Miyata, H., Kashimoto, T., and Kunita, N. Studies on the compounds related to PCB (V). Detection and determination of unknown organochlorinated compounds in Kanemi rice oil caused the Yusho. J. Food Hyg. Soc. Japan. 19: 364–371 (1978).
3. Nagayama, J., Masuda, Y., and Kuratsune, M. Chlorinated dibenzofurans in Kanechlors and rice oil used by patients with Yusho. Fukuoka Acta Med. 66: 593–599 (1975).
4. Yoshimura, H., Yoshihara, S., Ozawa, N., and Miki, M. Possible correlation between induction modes of hepatic enzymes by PCBs and their toxicity in rats. In: Health Effect of Halogenated Aromatic Hydrocarbons Annals of the New York Academy of Sciences, Vol. 320 (W. J. Nicholson and J. A. Moore, Eds.), New York Acad. Sci., New York, 1979, pp. 179–192.
5. McNulty, W. P., Becker, G. M., and Cory, H. T. Chronic toxicity of 3,4,3,4-and 2,5,2,5-tetrachlorobiphenyls in rhesus macaques. Toxicol. Appl. Pharmacol. 56: 182–190 (1980).
6. McKinney, J. D., Chae, K., Gupta, B. N., Moore, J. A., and Goldstein, J. A. Toxicological assessment of hexachlorobiphenyl isomers and 2,3,7,8-tetrachlorodibenzofuran in chicks. 1. Relationship of chemical parameters. Toxicol. Appl. Pharmacol. 36: 65–80 (1976).
7. Kashimoto, T., Miyata, H., and Kunita, N. The presence of polychlorinated quarterphenyls in the tissues of Yusho victims. Food Cosmet. Toxicol. 19: 335–340 (1981).
8. Nagayama, J., Masuda, Y., and Kuratsune, M. Determination of polychlorinated dibenzofurans in tissues of patients with Yusho. Food Cosmet. Toxicol. 15: 195–198 (1977).
9. Hori, S., Obana, H., Kashimoto, T., Otake, T., Nishimura, H., Ikegami, N., Kunita, N., and Uda, H. Effect of polychlorinated biphenyls and polychlorinated quarterphenyls in Cynomolgus monkey (*Macaca fascicularis*). Toxicology. 24: 123–139 (1982).
10. Shindo, U. Experimental Method of Immunology and Allegology. Kobundo, Tokyo, 1971, p. 305.
11. Otake, T., Takagi, Nishimura, H., Kataoka, M., Aburada, A., Akatani, K., Ikegami, N., and Kitaura, T. Effects of PCBs on Green monkeys. III. Effects of PCBs on immune responses. Osaka

Pref. Repts. Inst. Publ. Health, 18: 73–81 (1980).
12. Lowry, O. H., Rosebrough, J., Farr, A. L., and Randall, R. J. Protein measurement with the Folin phenol reagent. J. Biol. Chem. 193: 265–275 (1951).
13. Omura, T., and Sato, R. The carbon monoxide binding pigment of liver microsomes. J. Biol. Chem. 239: 2370–2378 (1964).
14. Hori, S., Obana, H., Kashimoto, T., Otake, T., Nishimura, H., Ikegami, N., Kunita, N., and Uda, H. Biological effect of compounds related to Yusho on female Cynomolgus monkeys. II. Studies on biochemical finding of blood, hepatic microsomal enzyme, immune response and histopathology. Osaka Pref. Repts. Inst. Publ. Health 12: 9–25 (1981).
15. Nebert, D. W., and Gelboin, H. V. Substrate-inducible microsomal aryl hydroxylase in mammalian cell culture. J. Biol. Chem. 243: 6242–6249 (1968).
16. Alvaes, A. P., Bickers, D. R., and Kappas, A. Polychlorinated biphenyls: a new type of inducer of cytochrome P-448 in the liver. Proc. Natl. Acad. Sci. (U.S.) 70: 1321–1325 (1973).
17. Goldstein, J. A., Hickman, P., Bergman, H., McKinney, J. D., and Walker, M. P. Separation of pure polychlorinated biphenyl isomers into two types of inducers on the basis of induction of cytochrome P-450 or P-448. Chem.-Biol. Interact. 17: 69–87 (1977).
18. Loose, L. D., Pittman, K. A., Bentitz, K. F., and Silkworth. J. B. Polychlorinated biphenyl and hexachlorobenzene induced humoral immunosuppression. J. Reticuloendo. Soc. 22: 253–271 (1977).
19. Thomas, P. T., and Hinsdill, R. D. Effect of polychlorinated biphenyls on the immune responses of rhesus monkeys and mice. Toxicol. Appl. Pharmacol. 44: 41–51 (1978).
20. Hayabuchi, H., Yoshimura, T., and Kuratsune, M. Consumption of toxic rice oil by Yusho patients and its relation to the clinical response and latent period. Food Cosmet. Toxicol. 17: 455–461 (1979).
21. Hara, I., Yakushiji, T., Kashimoto, T., and Kunita, N. Follow-up studies on the health status of the workers occupationally exposed to PCB and their children. In: Proc. 8th Int. Conf. Occup. Health Chem. Ind. (N. Takemura and Y. Yamamura, Eds.), Aikawa Shobo Publ. Co., Tokyo, 1980, pp. 312–316.
22. Hasegawa, H., Sato, M., and Tsuruta, H. PCB concentration in the blood of workers handling PCB. Rodo Eisei 13: 50–55 (1972).
23. Kashimoto, T., Miyata, R., Kunita, N., Tung, T., Hsu, S., Chang, K., Tang, S., Ohi, G., Nakagawa, J., and Yamamoto, S. Role of polychlorinated dibenzofuran in Yusho (PCB poisoning). Arch. Environ Health 36: 321–326 (1981).