

A Cohort Study on Mortality of "Yusho" Patients:
A Preliminary Report

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Abstract: In 1968, a mass food poisoning (Yusho) occurred in western Japan involving more than 1,850 people, the majority of whom were residents of Fukuoka and Nagasaki prefectures. The poisoning is now understood to have been caused by ingestion of a commercial brand of rice oil contaminated with polychlorinated derivatives of biphenyls, dibenzofurans, quaterphenyls, and some other related compounds. The number of deaths seen among 1,761 victims (887 males and 874 females) from the date of official registration as Yusho up to the end of 1983 was compared with the expected number of deaths which was calculated on the basis of the national age, sex, and cause-specific death rates. Neither significantly increased nor significantly decreased mortality was seen among overall causes of death in males and females. A significant excess mortality was seen for malignant neoplasms at all sites in males but not in females. Neither significantly increased nor decreased mortality was seen for cancer of the esophagus, stomach, rectum and colon, pancreas, breast, and uterus. For cancer of the liver, however, a considerably increased mortality was seen in both males and females but the excess was statistically significant only in males. It was also notable that such increased mortality due to liver cancer was seen mainly among the patients living in Fukuoka prefecture but not at all among those in Nagasaki prefecture which approximate the Yusho patients in Fukuoka prefecture in number. Deaths from chronic liver diseases and liver cirrhosis were also found to be increased in both sexes but the increase was not statistically significant.

Early in October 1968, an epidemic of a strange disease characterized by severe acne-like eruptions was reported in Fukuoka, Nagasaki, and other prefectures in western Japan. Epidemiologic and chemical investigations demonstrated that the epidemic was caused by ingestion of a commercial brand of rice oil contaminated with a complex mixture of polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), polychlorinated quaterphenyls (PCQs) and other related compounds (1-4). Figure 1 shows the chemical structures of these compounds and

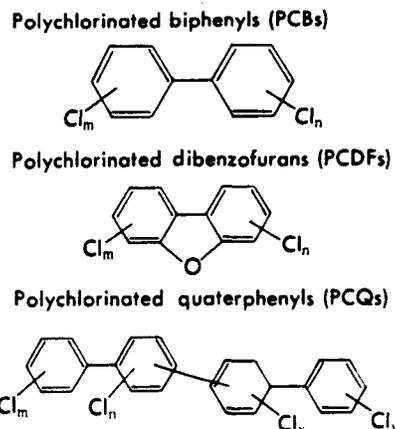


FIG. 1. Chemical structure of chlorinated hydrocarbons.

TABLE 1. Concentration of PCBs and Related Compounds in Samples of Toxic Rice Oil

Compound	No. of samples	Concentration (ppm)
Polychlorinated biphenyls (PCBs)	3	830, 900, 1,030 ^{a)}
Polychlorinated dibenzofurans (PCDFs)	3	5, 4, 5 ^{a)}
Polychlorinated quaterphenyls (PCQs)	2	705, 950 ^{b)}

^{a)} Ref. 5. ^{b)} Ref. 6.

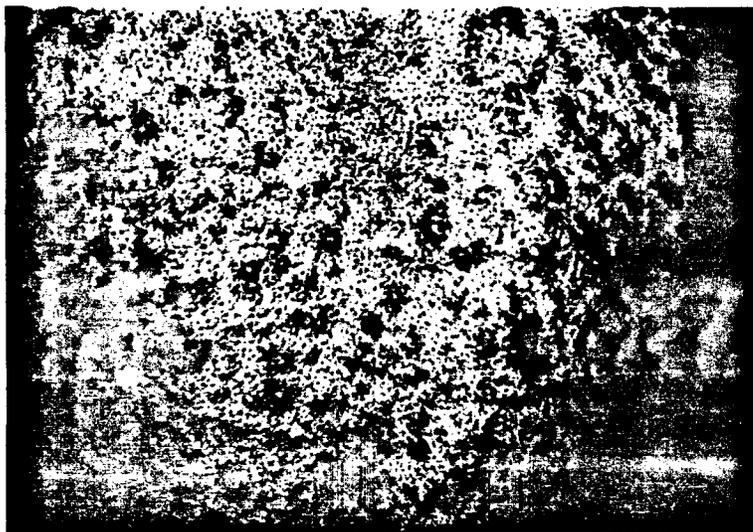


FIG. 2. Dermal lesions of Yusho patients.

Table 1 their concentration in the toxic rice oil consumed by patients. The disease was clinically diagnosed as chloracne and named "Yusho" which literally means "oil disease" in Japanese (Fig. 2).

The most notable manifestations of Yusho are dermal lesions such as comedo formation, acneform eruptions, hyperpigmentation, and hyperkeratosis (7). Peculiar

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ocular lesions such as swelled meibomian glands filled with yellow infarct-like material and pigmentation of the conjunctiva were also notable (8, 9). Most patients complained of various neurological symptoms such as headache, numbness of the limbs (10) and cough with sputum production for a prolonged period of time (11). Contrary to our expectation, patients showed few abnormalities of the liver in gross appearance or in liver function tests, but a marked proliferation of the smooth endoplasmic reticulum and a distinct reduction of the rough endoplasmic reticulum were noted by electron microscopy of liver biopsy specimens from one patient (12). During the 19 years since the poisoning, the above lesions have been very slow to improve and no complete recovery seems to have been attained yet in quite a few patients, as indicated by the fact that the subcutaneous adipose tissue samples from patients examined even 16 years after the onset of illness still contained, on average, 207 ppb of PCQs, which is more than 100 times the control level (13).

Cohort Analysis of Deaths

Analysis of deaths among the Yusho patients is important not only for better understanding of the health effects of prolonged exposure to these highly persistent man-made chlorinated hydrocarbons, but also for better health care. A cohort analysis was therefore made of the deaths (14).

The total number of patients officially registered as Yusho by the end of 1983

TABLE 2. Observed and Expected Numbers of Deaths and O/E Ratio by Cause of Death

Cause of death	Male			Female		
	Observed	Expected	O/E	Observed	Expected	O/E
All	79	66.13	1.19	41	48.90	0.84
Tuberculosis	1	1.26	0.79	0	0.50	0.00
Malignant neoplasms	33	15.51	2.13**	8	10.55	0.76
Esophagus	1	0.77	1.30	1	0.18	5.45
Stomach	8	5.69	1.40	0	3.26	0.00
Rectum, sigmoid colon, and anus	1	0.63	1.60	0	0.46	0.00
Liver	9	1.61	5.59**	2	0.66	3.04
Pancreas	1	0.71	1.41	1	0.46	2.18
Lung, trachea, and bronchus	8	2.45	3.26**	0	0.85	0.00
Breast	0	0.01	0.00	1	0.66	1.46
Uterus				1	0.58	1.71
Leukemia	1	0.45	2.23	0	0.32	0.00
Diabetes	1	0.75	1.34	0	0.69	0.00
Heart diseases	10	9.46	1.06	9	7.65	1.18
Hypertensive diseases	0	1.20	0.00	0	1.39	0.00
Cerebrovascular diseases	8	14.61	0.55	5	12.03	0.42*
Pneumonia and bronchitis	3	3.17	0.95	0	2.33	0.00
Gastric and duodenal ulcer	0	0.73	0.00	1	0.34	2.96
Chronic liver diseases and cirrhosis	6	2.26	2.65	2	0.73	2.74
Nephritis, nephrotic syndrome and nephrosis	0	0.79	0.00	2	0.71	2.81
Accidents	5	4.66	1.07	2	1.32	1.52

* $p < 0.05$, ** $p < 0.01$.

was 1,821. Information on name, date of birth, sex, address, and date and place of registration was obtained from the Ministry of Health and Welfare and the vital status of the registrants at the end of 1983 was confirmed by health departments of municipalities where they lived or still live; copies of the death certificates for decedents were also collected by these departments. Underlying causes of deaths seen before 1979 were assigned according to the 8th revision of ICD and deaths in 1979 and thereafter according to the 9th revision of ICD. Excluding 9 patients who had been officially registered as Yusho after death and 51 who were lost to follow-up, 1,761 patients (887 males and 874 females) were followed from the date of official registration to the end of 1983, the average duration of follow-up being about 11 years. The number of deaths during the observation period was compared with the expected number of deaths which was calculated by applying the national age, sex, and cause-specific death rates in 1970, 1975, and 1980 to the person-years at risk.

As shown in Table 2, the total number of deaths observed was 120, 79 males and 41 females. Male deaths were slightly more than expected but the difference was not statistically significant while females had fewer than expected, though again the difference was not statistically significant. Neither significantly elevated nor lowered mortality was seen for tuberculosis, diabetes, heart diseases, hypertensive diseases, pneumonia and bronchitis, gastric and duodenal ulcer, kidney diseases, or accidents. Deaths from cerebrovascular diseases were less than expected in both sexes, but significantly so only in females.

For deaths from cancer at all sites, a significantly increased mortality was seen in males but not in females. Neither significantly increased nor decreased mortality was seen for cancer of the esophagus, stomach, rectum and colon, pancreas, breast, and uterus, or leukemia. A significantly increased mortality was observed for cancer of the respiratory system in males but not in females.

For cancer of the liver (155, according to the 9th revision of ICD), 9 male deaths and 2 female deaths were observed and investigation of the clinical records of these decedents which is now in progress has so far demonstrated that at least 5 of them were from hepatoma. A marked excess of these deaths was observed in males, with an O/E (observed/expected) ratio as high as 5.59, and a less marked excess (O/E ratio=3.04) was also seen in females; the excess was statistically significant, however, only in males. Since about 45% and 40% of the patients are residents of Fukuoka and Nagasaki prefectures, respectively, where liver cancer is known to be the highest in the nation, an additional analysis was made by calculating expected number of deaths on the basis of liver cancer death rates in these prefectures instead of using the national average death rates. Again, a significantly increased mortality was observed in males (observed=9, expected=2.34, O/E ratio=3.85, $p < 0.01$) but not in females (observed=2, expected=0.79, O/E ratio=2.53). In view of the long latent period common in the development of cancer, cancer cases which occurred soon after poisoning can hardly be regarded as having been caused by the poisoning alone. Excluding such cases, 4 deaths from liver cancer among males which occurred in Fukuoka prefecture more than 9 years after the onset of poisoning were compared with the corresponding expected number of deaths calculated from the male death rates there for this cancer. Again, a statistically significant excess mortality was seen (observed=4, expected=1.04, O/E ratio=3.85, $p < 0.05$). Further-

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more, not only deaths from liver cancer, but also deaths from chronic liver diseases and cirrhosis were found to be slightly increased in both males and females, although the increase was not statistically significant. Investigation of medical records has so far revealed that 2 of the 9 decedents from liver cancer had been infected with HB virus and only one had been a heavy drinker of alcohol.

The above findings suggest that the poisoning might have caused liver cancer at least in male patients. However, it seems still too early to draw any definite conclusion on this issue, because, as mentioned, contrary to the experience in Fukuoka prefecture, no excess death from liver cancer was seen in either male or female patients in Nagasaki prefecture where approximately the same number as in Fukuoka prefecture developed Yusho. Such a markedly uneven geographical distribution of deaths can hardly be explained by exposure to the toxic rice oil alone. Our findings should not be disregarded, however, because the hepatocarcinogenicity of PCBs in animals has been well documented (15, 16).

REFERENCES

1. Kuratsune, M., Yoshimura, T., Matsuzaka, J., and Yamaguchi, A. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls: Environ. Health Perspect. Exp. Issue, 5: 119-128, 1972.
2. Nagayama, J., Kuratsune, M., and Masuda, Y. Determination of chlorinated dibenzofurans in Kanechlors and 'Yusho Oil'. Bull. Environ. Contamin. Toxicol., 15: 9-13, 1976.
3. Miyata, H., Murakami, Y., and Kashimoto, T. Studies on the compounds related to PCB (VI). Determination of polychlorinated quaterphenyl (PCQ) in Kanemi rice oil caused the "Yusho" and investigation on the PCQ formation. J. Food Hyg. Soc., 19: 417-425, 1978.
4. Kashimoto, T., Miyata, H., Takayama, K., and Ogaki, J. Levels of PCDDs, coplanar PCBs and PCDFs in patients with Yusho and the causal oil by HR-GC. HR-MS. Fukuoka Acta Med., 78: 325-336, 1987 (in Japanese).
5. Nagayama, J., Masuda, Y., and Kuratsune, M. Chlorinated dibenzofurans in Kanechlors and rice oils used by patients with Yusho. Fukuoka Acta Med., 66: 593-599, 1975.
6. Yamaguchi, S. and Masuda, Y. Quantitative analysis of polychlorinated quaterphenyls in Yusho oil by high performance liquid chromatography. Fukuoka Acta Med., 76: 132-136, 1985 (in Japanese).
7. Urabe, H. and Asahi, M. Past and current dermatological status of Yusho patients. Environ. Health Perspect., 59: 11-15, 1985.
8. Ikui, H., Sugi, K., and Uga, S. Ocular signs of chronic chlorobiphenyls poisoning (Yusho). Fukuoka Acta Med., 60: 432-439, 1969 (in Japanese).
9. Kohno, T. and Ohnishi, Y. Ocular manifestations and polychlorinated biphenyls in the tarsal gland contents of Yusho patients. Fukuoka Acta Med., 76: 244-247, 1985 (in Japanese).
10. Nagamatsu, K. and Kuroiwa, Y. Electroencephalographical studies on 20 patients with chlorobiphenyl poisoning. Fukuoka Acta Med., 62: 157-158, 1971 (in Japanese).
11. Nakanishi, Y., Shigematsu, N., Kurita, Y., Matsuba, K., Kanegae, H., Ishimaru, S.,

- and Kawazoe, Y. Respiratory involvement and immune status in Yusho patients. *Environ. Health Perspect.*, *59*: 31-36, 1985.
12. Hirayama, C., Iriya, T., and Yamamoto, T. Fine structural changes of the liver in a patient with chlorobiphenyl intoxication. *Fukuoka Acta Med.*, *60*: 455-461, 1969 (in Japanese).
 13. Ohgami, T., Nonaka, S., Yoshida, H., Maruyama, F., Yamashita, K., and Masuda, N., PCB, PCQ concentration of blood and subcutaneous tissue in patients with PCB poisoning (Yusho). *Fukuoka Acta Med.*, *78*: 337-342, 1987 (in Japanese).
 14. Ikeda, M., Kuratsune, M., Nakamura, Y., and Hirohata, T. A cohort study on mortality of Yusho patients—A preliminary report. *Fukuoka Acta Med.*, *78*: 297-300, 1986.
 15. Kimura, H. and Baba, T. Neoplastic change in the rat liver induced by polychlorinated biphenyls. *Gann*, *64*: 105-108, 1973.
 16. Ito, N., Nagasaki, H. J., Makiura, S., and Arai, M. Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. *Gann*, *65*: 545-549, 1974.