American Journal of Epidemiology
Vol. 169, No. 1
DOI: 10.1093/aje/kwn295
Advance Access publication October 30, 2008

Original Contribution

Mortality After Exposure to Polychlorinated Biphenyls and Polychlorinated Dibenzofurans: A 40-Year Follow-up Study of Yusho Patients

Daisuke Onozuka, Takesumi Yoshimura, Satoshi Kaneko, and Masutaka Furue

Initially submitted July 1, 2008; accepted for publication August 14, 2008.

A 40-year follow-up study was conducted to examine mortality among 1,664 patients in Japan suffering from "Yusho," a disease caused by ingestion of rice oil contaminated with polychlorinated biphenyls and polychlorinated dibenzofurans. To evaluate the effects of exposure on mortality, the authors calculated standardized mortality ratios. National mortality rates for major causes of death were used as reference points. A total of 1,596 Yusho patients (95.9%) were followed until death or the end of the study (December 31, 2007). The standardized mortality ratios for most major causes of death were not significantly elevated, with the exceptions of all types of cancer (standardized mortality ratio (SMR) = 1.37, 95% confidence interval (CI): 1.11, 1.66), liver cancer (SMR = 1.82, 95% CI: 1.06, 2.91), and lung cancer (SMR = 1.75, 95% CI: 1.14, 2.57) in males. In addition, the standardized mortality ratios for all cancers, liver cancer, and lung cancer among males tended to decrease over time. Results from this study suggest that the carcinogenicity of polychlorinated biphenyls and polychlorinated dibenzofurans must be taken into account when evaluating mortality risk.

cohort studies; food contamination; mortality; neoplasms; polychlorinated biphenyls

Abbreviations: CDF, chlorinated dibenzofuran; CI, confidence interval; ICD, *International Classification of Diseases*; PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran; SMR, standardized mortality ratio.

In 1968, a mass accidental exposure to dioxin-like compounds occurred in western Japan through the ingestion of a contaminated commercial brand of rice oil (1). The contaminants consisted of at least 74 different polychlorinated biphenyl (PCB) compounds and 47 congeners of tetra- through octa-polychlorinated dibenzofuran (PCDF) (1). As a result, approximately 1,800 patients suffered a range of symptoms, including acneiform eruptions; pigmentation of the skin, nails, and conjunctiva; increased discharge from the eyes; and numbness of the limbs. The syndrome resulting from this mass poisoning was named "Yusho," which means "oil disease" in Japanese (1). In 1979, a similar incident occurred in central Taiwan (referred to as the Yucheng incident; "Yucheng" is "oil disease" in Chinese), in which approximately 2,000 individuals consumed contaminated rice oil and developed similar symptoms (2). In both incidents, PCBs used as heat exchangers contaminated rice bran cooking oil during processing. These PCBs had been thermally degraded and were thus contaminated by PCDFs (1, 2). Thus, these incidents have subsequently been used for the evaluation of adverse and prolonged health effects associated with PCB and PCDF ingestion.

On the basis of evidence from animal studies, PCBs are considered potentially carcinogenic to humans. However, the results of studies in human populations exposed to PCBs have been inconsistent. Follow-up studies of workers exposed to PCBs suggested inconsistent association with elevated mortality rates for malignant melanoma (3–5); brain cancer (3–5); gastrointestinal cancer (4, 6–8); cancer of the biliary tract, liver, and gallbladder (4, 8–12); cancer of the hematopoietic system (4, 6, 11, 12); and prostate cancer (8, 13). Cardiovascular disease, diabetes, and autoimmune disease mortality were not found increased in most of the above studies. In addition, follow-up of occupational cohorts exposed to polychlorinated dibenzodioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, and PCDFs suggested

Correspondence to Dr. Daisuke Onozuka, Department of Information Science, Fukuoka Institute of Health and Environmental Sciences, 39 Mukaizano, Dazaifu-shi, Fukuoka 818-0135, Japan (e-mail: onozuka@fihes.pref.fukuoka.jp).

increased cancer mortality (14–19). Significant cause-specific cancer mortalities were reported for rectal cancer (16), laryngeal cancer (15), bladder cancer (15), lung cancer (14, 16–18), soft tissue sarcoma (14, 20), and lymphatic and hematopoietic cancer (15, 16). Although the Seveso cohort exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin failed to exhibit a significant increase in all-cancer mortality, mortality was increased from lymphatic and hematopoietic cancers (21, 22). Mortality from circulatory diseases was increased in the Ranch Hand Cohort Study (19). Mortality from diabetes and chronic obstructive pulmonary disease was found to be increased in the Seveso cohort (21, 22).

In the Japanese Yusho population exposed to PCBs and PCDFs, results of several investigations have been published since the incident. PCB concentrations in the adipose tissue of Yusho patients were estimated to have reached 46–76 ppm (wet weight basis; concentration of the analytes reported based on the sample's wet weight) soon after the incident (23). Adipose PCB concentrations decreased rapidly to 2-fold or 3-fold those of the general population 1–2 years after the incident and remained elevated until recent years (24). The concentrations of residual PCDFs in the blood and adipose tissue of Yusho patients 20 years after exposure remained 3-fold to 64-fold greater than those of the general population (25). Preliminary follow-up studies conducted in 1983 and 1990 were reported in 1987 and 1996, respectively. These studies showed that the standardized mortality ratios for liver cancer and lung cancer had increased in male incident victims compared with those in the general Japanese population (26, 27). Mortality caused by chronic liver disease was found increased at a statistically nonsignificant level (26, 27). However, there were 2 key problems with the interpretation. First, the standardized mortality ratio for liver cancer decreased by approximately 40% between 1983 and 1990, and second, in the Yucheng incident, the standardized mortality ratio for liver cancer did not increase, whereas that for liver cirrhosis did (28, 29). The last evaluation of the Yusho-poisoned cohort was conducted more than 10 years ago, and that update left some open questions regarding the effects of PCBs and PCDFs on hepatic and other adverse mortality effects.

In this study, we updated follow-up study data for Yusho patients and reevaluated the mortality in the Yusho cohort 40 years after exposure to PCBs and PCDFs. This study advances knowledge about mortality effects by adding substantial follow-up time.

MATERIALS AND METHODS

The total number of Yusho patients listed in the Yusho case register as of December 31, 2007, was 1,918 (977 males and 941 females). Among 1,918 Yusho patients, 254 cases who were registered in the list after 1977 were excluded from the analysis, because those have not been diagnosed as Yusho from the beginning of the Yusho incident. Because the designation procedures of Yusho were revised several times after the Yusho incident, these factors could have caused us to miss potentially affected patients who died prior to the official registration period and to potentially introduce bias into this study. Thus, we analyzed a total of 1,664 cases (86.8% of Yusho patients) as Yusho cohort subjects. The members of this cohort did not receive any special care (such as more frequent medical screenings) that could have resulted in early diagnoses of diseases and therefore less mortality.

The subjects were identified by name, date of birth, sex, address, and date and place of registration. Follow-up surveys to determine vital status were conducted with the cooperation of the municipal health departments overseeing the regions in which the Yusho patients had lived or were still living. Residency and death registration are required by Family Registration Law in Japan and were believed to be complete across Japan. Details regarding the underlying causes of death were collected by transcribing copies of death certificates archived in regional public health centers and reported to the Ministry of Health, Labour, and Welfare, Japan.

The underlying causes of death identified in the survey were ascertained by record linkage (i.e., matching the follow-up data with the national vital statistics). This method has been shown to be a reliable and valid manner of tracing a target person (30). Death certificate diagnoses were provided by the Ministry of Health, Labour, and Welfare under special permission from the Statistics Bureau of the Ministry of Internal Affairs and Communications of Japan. The underlying causes of death were defined according to the *International Classification of Diseases* (ICD), Eighth Revision, for certificates issued before 1979; the ICD, Ninth Revision, for certificates issued between 1979 and 1994; and the ICD, Tenth Revision, for certificates issued in 1995 and later for national vital statistics. Therefore, all deaths that occurred in the cohort were confirmed by death certificates from a public health center, except for subjects who died after they moved from their original community, in which case the subject was treated as a censored case. In the case of successful linkage, we obtained the ICD death codes. To ensure compatibility with mortality rates, all death codes were translated to the Ninth Revision codes.

We calculated the person-years at risk for each Yusho patient from the patient's official registration date to one of the following dates, selected according to vital status: the date of death, the last vital status confirmation date for those lost to follow-up, or December 31, 2007, for those who had completed the follow-up. We chose the official registration date as a starting date for calculating person-years because the detection of affected individuals was difficult at the time of exposure; the distribution of the contaminated rice oil was broad and scattered throughout western Japan, and it was technically impossible to measure PCBs and PCDFs in the human body at the time of the incident. Thus, we may have missed potential person-years between the exposure date and the registration date, and some affected individuals who survived might not have been identified. We divided person-years for the patients into gender, calendar period, and age categories. We calculated the expected number of deaths by using cause-specific mortality rates specific for cause of death, sex, 5-year calendar periods, and 5-year age classes (31).

We used an age-modified method to calculate standardized mortality ratios, according to sex and cause of death, by

Table 1. Distribution of Age in 1968 and Vital Status in 2007 of the Japanese Yusho Cohort

	Males (n = 860)		Females (n = 804)	
	No.	%	No.	%
Age in 1968, years				
<20	345	40.1	305	37.9
20–29	94	10.9	99	12.3
30–39	126	14.7	136	16.9
40–49	140	16.3	130	16.2
50–59	82	9.5	68	8.5
60–69	49	5.7	43	5.3
70–79	20	2.3	21	2.6
≥80	4	0.5	2	0.2
Vital status on December 31, 2007				
Alive	591	68.7	632	78.6
Dead	269	31.3	172	21.4
Person-years of follow-up	25,292		25,481	

dividing the number of observed deaths by the number of expected deaths in each calendar period. The 95% confidence interval was calculated for each standardized mortality ratio, assuming that the number of observed deaths was a Poisson distribution and that the expected value was known without error. All analyses were conducted by using SAS, version 8.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 1,596 Yusho patients (95.9%) were followed up until death or the end of the study (December 31, 2007). Table 1 shows the distribution of age in 1968 and vital status in 2007 among the Yusho cohort. As of December 31, 2007, a total of 1,664 Yusho cases (860 males and 804 females) with 50,773 person-years (25,292 person-years for males and 25,481 person-years for females) were at risk. Approximately 39% of the cohort was under 20 years of age in 1968. The mean age of Yusho patients alive in 2007 was 57.9 (standard deviation, 14.1) years in males and 61.3 (standard deviation, 15.2) years in females. A total of 441 deaths (269 males and 172 females) occurred during the 40-year follow-up period.

Tables 2–4 show the observed and expected numbers of deaths, standardized mortality ratios, and 95% confidence intervals for the major causes of death among the Yusho patients between 1968 and 2007. Over the entire study period, the male and female standardized mortality ratios for all-cause mortality were not significantly elevated compared with those in the Japanese general population (Table 2). Significant elevations occurred among males for all cancers (standardized mortality ratio (SMR) = 1.37, 95% confidence interval (CI): 1.11, 1.66) and for lung cancer (SMR = 1.75, 95% CI: 1.14, 2.57). Among females, the standardized mortality ratio for stomach cancer (SMR = 0.22, 95% CI: 0.03, 0.81) was decreased. The standardized

Table 2. Observed and Expected Number of Deaths, Standardized Mortality Ratios, and 95% Confidence Intervals for the Major Causes of Death Among Japanese Yusho Patients Between 1968 and 2007

Cause of Death (ICD-9 Codes)	Males				Females			
	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval
All causes (001–999)	269	238.3	1.13	1.00, 1.27	172	170.8	1.01	0.86, 1.17
All cancers (140–208)	100	73.1	1.37	1.11, 1.66	33	44.3	0.75	0.51, 1.05
Stomach (151)	20	17.1	1.17	0.72, 1.81	2	8.9	0.22	0.03, 0.81
Rectum (154)	2	3.1	0.65	0.08, 2.36	1	1.8	0.56	0.01, 3.10
Liver (155)	17	9.4	1.82	1.06, 2.91	7	3.6	1.95	0.78, 4.01
Pancreas (157)	6	4.0	1.49	0.55, 3.24	3	2.9	1.02	0.21, 2.98
Lung (162)	26	14.8	1.75	1.14, 2.57	4	4.9	0.82	0.22, 2.11
Breast (174)	0	0.0			3	3.2	0.93	0.19, 2.72
Uterus (179–182)					3	2.6	1.14	0.24, 3.33
Leukemia (204–208)	2	1.7	1.19	0.14, 4.29	0	1.1	0.00	0.00, 3.25
Diabetes mellitus (250)	1	2.9	0.35	0.01, 1.94	2	2.5	0.79	0.10, 2.83
Hypertension (401–405)	2	2.2	0.92	0.11, 3.32	1	2.7	0.37	0.01, 2.08
Heart disease (393–398, 410–429)	38	36.0	1.06	0.75, 1.45	34	30.0	1.13	0.78, 1.58
Cerebrovascular disease (430–438)	34	36.3	0.94	0.65, 1.31	32	31.8	1.01	0.69, 1.42
Hepatic disease (570–573)	11	6.7	1.63	0.81, 2.92	4	2.8	1.42	0.39, 3.64

Abbreviation: ICD-9, *International Classification of Diseases*, Ninth Revision.

mortality ratio for liver cancer was elevated in both males and females (males: SMR = 1.82, 95% CI: 1.06, 2.91; females: SMR = 1.95, 95% CI: 0.78, 4.01). Non-cancer-related mortality did not differ from that in the background population.

We compared the number of observed and expected deaths for each major cause of death in eight 5-year intervals since the incident (Tables 3 and 4). Among males, the standardized mortality ratios for all cancers, liver cancer, and lung cancer were elevated during the first 5 years (0–4 years), with standardized mortality ratio estimates of 3.31 (95% CI: 1.21, 7.20), 6.22 (95% CI: 0.16, 34.65), and 5.13 (95% CI: 0.13, 28.58), respectively. However, such an increase in the standardized mortality ratio was not seen after the fourth 5-year period. Among females, we did not observe meaningful increases (or decreases) in the standardized mortality ratios for the major causes of death in any calendar-year category, with the exception of heart disorders 25–29 years after the incident (SMR = 2.40, 95% CI: 1.15, 4.41).

DISCUSSION

Several notable points were shown by our findings. Most importantly, our results suggest that male Yusho patients showed elevated mortality from all types of cancers, liver cancer, and lung cancer in particular in comparison with the general population (Table 2). These causes of death were found to be increased in the early period after the Yusho accident in exposed males but not in females. This result possibly may be due to the differential effects of some of the endocrine-disrupting PCBs and PCDFs in males and females. The data also suggested possible increases in mortality from other cancer (stomach cancer in males) and other diseases (heart disease in females). These results were informative because the power of this study to detect changes continues to increase with continued long-term follow-up.

Mortality from all cancers among males was significantly elevated throughout the follow-up period. The magnitude of this increase was similar to that estimated in previous long-term studies on high-exposure male cohorts (16, 20). Our results suggest that exposure to PCBs and PCDFs may result in an excess of all cancers among males, which is consistent with previous reports (16, 17, 19). However, among Yucheng cases, mortality from all malignant neoplasms was not different from that for the general population (28, 29).

Lung cancer mortality was also elevated among males throughout the follow-up period. Several independent studies examining male cohorts with biologically documented exposure to high levels of dioxin detected an elevated risk of lung cancer (14, 16, 17). On the other hand, mortality from lung cancer among the Yucheng cases was not different from that for the general population (28, 29). The lung is one of the target organs of the carcinogenic action of dioxins in animals (32). Although we did not have individual data on smoking habits, homogeneity in educational and cultural features among the Yusho patients and the general population makes systematic differences quite improbable. A second indicator that individual smoking habits did not affect mortality is that other smoking-related cancers did not increase.

Gastric and rectal cancer mortality showed no increases during any interval of the follow-up period. Indeed, little experimental evidence exists of a relation between dioxin exposure and such digestive-type cancers, although an increase in these cancers was noted in previous occupational cohort studies in Germany and New Zealand (33). Colorectal cancer was also increased in Seveso males (21, 22).

We also did not detect an increase in breast or uterine cancers. These results are consistent with previous findings of mortality investigations on PCBs and PCDFs. However, recent case-control studies in selected samples of the Seveso incident population suggested a positive association with breast cancer (34) and a negative association with uterine cancer (35). A recent updated study of the mortality of the whole Seveso population suggested no excess of breast and other gynecologic cancers (22). Other gender-specific effects recently examined in relation to well-established endocrine disruptors (36) were endometriosis and ovarian function; however, no association was found (37).

Although the results of previous experimental studies indicated an association between dioxin exposure and leukemia (38), we observed 2 cases of leukemia among our subjects. Previous studies suggested the increased cancer mortalities of soft tissue sarcoma (14, 20) and lymphatic and hematopoietic cancer (15, 16, 21, 22). However, hypothesizing about systematic differences between the exposed and general populations is difficult in terms of exposure to known biologic, chemical, or radiologic risk factors for hematologic neoplasms (39).

The standardized mortality ratio for liver cancer was elevated in both males and females (males: SMR = 1.82, 95% CI: 1.06, 2.91; females: SMR = 1.95, 95% CI: 0.78, 4.01). Furthermore, the standardized mortality ratio for hepatic disease was also increased in both sexes (males: SMR = 1.63, 95% CI: 0.81, 2.92; females: SMR = 1.42, 95% CI: 0.39, 3.64). These results are consistent with those of previous studies on the Yusho patients (26, 27). However, the standardized mortality ratios for malignant and nonmalignant hepatic diseases in these patients showed only insignificant increases during the recent intervals. Thus, we cannot ascertain whether prolonged exposure to PCBs and PCDFs at the observed levels is carcinogenic. Among the Yucheng population, excess mortality due to liver cancer was not reported among patients exposed to PCBs and PCDFs, whereas liver cirrhosis mortality was (28, 29). This difference may be due to misclassification of diagnoses between liver cancer and liver diseases (40). The potential misclassification bias, if any, is likely to induce or reduce the relative risk for malignant and nonmalignant hepatic diseases. Hence, any residual misclassification between liver cancer and hepatic disease may lead to overestimation of the liver cancer risk. Moreover, Japan has the highest rate of liver cancer in any industrialized country, and the annual number of death cases is expected to rise above 34,000 over the next 10 years, according to a report by the Japan Society of Hepatology. In 2002, the mortality rate of liver cancer among males and females in Japan was 38.7 cases per 100,000 individuals and 16.8 cases per 100,000 individuals,

Table 3. Observed and Expected Numbers of Deaths, Standardized Mortality Ratios, and 95% Confidence Intervals for Major Causes of Death Among Male Japanese Yusho Patients in Each 5-Year Interval From 1968 to 2007

Cause of Death (ICD-9 Codes)	No. of Years Since the Accident															
	0–4 (1968–1972)				5–9 (1973–1977)				10–14 (1978–1982)				15–19 (1983–1987)			
	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval
All causes (001–999)	16	9.8	1.64	0.94, 2.66	28	21.2	1.32	0.88, 1.91	30	28.2	1.07	0.72, 1.52	43	30.0	1.43	1.04, 1.93
All cancers (140–208)	6	1.8	3.31	1.21, 7.20	10	4.6	2.18	1.05, 4.01	15	7.2	2.08	1.17, 3.44	11	8.7	1.26	0.63, 2.25
Stomach (151)	3	0.8	3.80	0.78, 11.10	6	1.8	3.31	1.22, 7.21	1	2.4	0.42	0.01, 2.35	2	2.4	0.84	0.10, 3.04
Rectum (154)	0	0.1	0.00	0.00, 55.04	0	0.2	0.00	0.00, 20.05	0	0.3	0.00	0.00, 12.50	0	0.4	0.00	0.00, 10.21
Liver (155)	1	0.2	6.22	0.16, 34.65	2	0.4	4.84	0.59, 17.50	4	0.8	4.99	1.36, 12.77	1	1.2	0.86	0.02, 4.79
Pancreas (157)	0	0.1	0.00	0.00, 51.74	0	0.2	0.00	0.00, 19.11	1	0.4	2.82	0.07, 15.73	1	0.5	2.09	0.05, 11.65
Lung (162)	1	0.2	5.13	0.13, 28.58	1	0.6	1.60	0.04, 8.90	3	1.2	2.57	0.53, 7.51	5	1.6	3.07	1.00, 7.17
Breast (174)	0	0.0			0	0.0			0	0.0			0	0.0		
Uterus (179–182)																
Leukemia (204–208)	0	0.1	0.00	0.00, 50.69	0	0.1	0.00	0.00, 25.88	1	0.2	5.32	0.13, 29.64	1	0.2	4.65	0.12, 25.93
Diabetes mellitus (250)	0	0.1	0.00	0.00, 38.42	1	0.3	3.93	0.10, 21.90	0	0.3	0.00	0.00, 12.13	0	0.3	0.00	0.00, 11.06
Hypertension (401–405)	0	0.2	0.00	0.00, 20.87	0	0.5	0.00	0.00, 8.11	0	0.5	0.00	0.00, 8.16	1	0.3	2.94	0.07, 16.35
Heart disease (393–398, 410–429)	2	1.1	1.87	0.23, 6.75	5	2.8	1.78	0.58, 4.15	2	4.6	0.43	0.05, 1.56	8	5.2	1.53	0.66, 3.02
Cerebrovascular disease (430–438)	1	2.2	0.46	0.01, 2.53	6	5.0	1.21	0.44, 2.63	1	5.8	0.17	0.00, 0.96	9	4.7	1.90	0.87, 3.60
Hepatic disease (570–573)	2	0.3	6.09	0.74, 21.99	0	0.8	0.00	0.00, 4.54	3	1.1	2.73	0.56, 7.97	1	1.1	0.90	0.02, 5.03
	20–24 (1988–1992)				25–29 (1993–1997)				30–34 (1998–2002)				35–39 (2003–2007)			
	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval
All causes (001–999)	40	32.3	1.24	0.88, 1.68	32	37.4	0.86	0.59, 1.21	47	40.7	1.16	0.85, 1.54	33	38.8	0.85	0.59, 1.20
All cancers (140–208)	14	10.3	1.36	0.74, 2.28	11	12.8	0.86	0.43, 1.54	16	14.3	1.12	0.64, 1.81	17	13.3	1.28	0.74, 2.04
Stomach (151)	4	2.4	1.70	0.46, 4.35	1	2.5	0.39	0.01, 2.19	3	2.6	1.15	0.24, 3.35	0	2.2	0.00	0.00, 1.67
Rectum (154)	1	0.4	2.32	0.06, 12.91	1	0.5	1.83	0.05, 10.17	0	0.6	0.00	0.00, 6.16	0	0.6	0.00	0.00, 6.47
Liver (155)	2	1.5	1.34	0.16, 4.83	4	1.9	2.12	0.58, 5.43	2	1.9	1.07	0.13, 3.85	1	1.6	0.64	0.02, 3.56
Pancreas (157)	1	0.6	1.72	0.04, 9.58	0	0.7	0.00	0.00, 5.13	1	0.8	1.22	0.03, 6.77	2	0.8	2.46	0.30, 8.87

Lung (162)	2	2.1	0.94	0.11, 3.39	3	2.7	1.10	0.23, 3.22	4	3.2	1.24	0.34, 3.19	7	3.2	2.21	0.89, 4.56
Breast (174)	0	0.0			0	0.0			0	0.0			0	0.0		
Uterus (179–182)																
Leukemia (204–208)	0	0.2	0.00	0.00, 15.90	0	0.3	0.00	0.00, 13.99	0	0.3	0.00	0.00, 12.50	0	0.3	0.00	0.00, 13.50
Diabetes mellitus (250)	0	0.3	0.00	0.00, 10.65	0	0.5	0.00	0.00, 6.71	0	0.5	0.00	0.00,7.21	0	0.5	0.00	0.00, 7.73
Hypertension (401–405)	0	0.2	0.00	0.00, 16.22	0	0.2	0.00	0.00, 17.02	0	0.2	0.00	0.00, 22.03	1	0.1	7.09	0.18, 39.48
Heart disease (393–398, 410–429)	7	5.9	1.19	0.48, 2.46	3	5.2	0.58	0.12, 1.69	7	5.6	1.24	0.50, 2.56	4	5.6	0.72	0.20, 1.83
Cerebrovascular disease (430–438)	3	4.1	0.73	0.15, 2.13	6	5.1	1.17	0.43, 2.55	6	5.0	1.20	0.44, 2.62	2	4.3	0.46	0.06, 1.66
Hepatic disease (570–573)	2	1.0	1.92	0.23, 6.94	2	0.9	2.30	0.28, 8.30	1	0.8	1.25	0.03, 6.94	0	0.7	0.00	0.00, 5.39

Abbreviation: ICD-9, *International Classification of Diseases*, Ninth Revision.

respectively (41). In addition, the mortality rate of chronic liver disease and cirrhosis among males and females was 15.2 per 100,000 and 6.4 per 100,000, respectively (41). The Yusho population was concentrated in the Chugoku and Kyushu areas, which are in the western part of Japan (26). Although the carrier rates of hepatitis C virus infection were from 2-fold to 3-fold higher in western Japan (42), there is no reason to suspect that Yusho patients had a higher carrier rate than did the background population. The similar liver cancer mortalities between the fourth and the eighth periods suggested carrier rates among Yusho patients similar to those of the background population in Japan.

Regarding non-cancer-related deaths, we observed increased mortality from heart disease among females 25–29 years after the incident, but with different patterns of latency. This association was not apparent over the entire follow-up period. The occurrence of such unexpected circulatory disease mortality late in the post-incident period (during 1993–1997) suggests another possibly relevant determinant, the miscoding and misclassification of heart disease mortality. The claims about miscertification are supported by the dramatic increase in recorded heart disease mortality rates in Japan between 1994 and 1995 (more than 25%) with the change from ICD, Ninth Revision, to ICD, Tenth Revision, whereby physicians were encouraged not to use heart failure as an underlying cause of death (43, 44). Other studies have suggested that miscertification of heart disease is common in Japan but have not proposed methods to adjust rates (45–47). In addition, because the heart disease mortality rate did not increase sharply shortly after the Yusho incident, it is unlikely that the epidemiology of heart disease could have changed sharply 25–29 years after the Yusho incident (in 1993–1997). Thus, the implementation of the ICD, Tenth Revision, may account for part of the change.

As for the exposures, it was found that the dose-response relation is quite different between Yusho/Yucheng patients and workers occupationally exposed to PCBs, when PCB levels in blood were taken as a common indicator of exposure intensity; the clinical manifestations were much severer in the former than in the latter, even when blood PCB levels were comparable (48). Despite the difference in time and place of outbreak as well as in the PCB preparations used, the overall clinical picture of Yusho was very similar to that of Yucheng, even though nail deformity of newborn babies might be more frequently observed in Yucheng than in Yusho (2). The total amounts of PCBs ingested by Yusho patients in the exposure period were estimated to be 2 g on average, and 0.5 mg was considered to be the minimum toxic dose (1). On the basis of body weight and daily intake, the minimal toxic dose was estimated to be 70 μg/kg per day at first but later reestimated to be 35 μg/kg per day or even less (49). In Yucheng, the estimated total intake by patients in the exposure period was 0.8–1.8 g on average (2), which was essentially the same as the dose for Yusho patients. In addition, the composition of PCDF isomers also differed markedly between the 2 incidents. The main isomer of PCDFs in Yusho patients was 2,3,4,7,8-penta-chlorinated dibenzofuran (CDF), which has the highest toxic equivalency factor among PCDFs (50). In Yucheng patients, the

Table 4. Observed and Expected Numbers of Deaths, Standardized Mortality Ratios, and 95% Confidence Intervals for Major Causes of Death Among Female Japanese Yusho Patients in Each 5-Year Interval From 1968 to 2007

Cause of Death (ICD-9 Codes)	No. of Years Since the Accident															
	0–4 (1968–1972)				5–9 (1973–1977)				10–14 (1978–1982)				15–19 (1983–1987)			
	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval
All causes (001–999)	6	8.1	0.74	0.27, 1.61	13	14.9	0.87	0.46, 1.49	19	18.8	1.01	0.61, 1.58	18	21.5	0.84	0.50, 1.32
All cancers (140–208)	3	1.5	2.03	0.42, 5.94	1	3.2	0.31	0.01, 1.73	0	4.5	0.00	0.00, 0.82	4	5.3	0.75	0.20, 1.92
Stomach (151)	0	0.5	0.00	0.00, 6.99	0	1.0	0.00	0.00, 3.53	0	1.3	0.00	0.00, 2.90	0	1.3	0.00	0.00, 2.87
Rectum (154)	0	0.1	0.00	0.00, 63.42	0	0.1	0.00	0.00, 25.35	0	0.2	0.00	0.00, 19.42	0	0.2	0.00	0.00, 16.55
Liver (155)	1	0.1	11.02	0.28, 61.40	0	0.2	0.00	0.00, 19.31	0	0.3	0.00	0.00, 13.79	1	0.4	2.77	0.07, 15.46
Pancreas (157)	0	0.0	0.00	0.00, 77.31	0	0.1	0.00	0.00, 27.96	0	0.2	0.00	0.00, 16.96	0	0.3	0.00	0.00, 11.97
Lung (162)	0	0.1	0.00	0.00, 46.95	0	0.2	0.00	0.00, 17.29	0	0.4	0.00	0.00, 9.77	1	0.5	1.89	0.05, 10.51
Breast (174)	1	0.1	12.31	0.31, 68.56	0	0.2	0.00	0.00, 17.97	0	0.3	0.00	0.00, 11.96	0	0.4	0.00	0.00, 9.97
Uterus (179–182)	0	0.2	0.00	0.00, 19.81	1	0.3	2.90	0.07, 16.18	0	0.4	0.00	0.00, 9.81	0	0.4	0.00	0.00, 10.45
Leukemia (204–208)	0	0.1	0.00	0.00, 66.23	0	0.1	0.00	0.00, 35.36	0	0.1	0.00	0.00, 28.82	0	0.1	0.00	0.00, 25.31
Diabetes mellitus (250)	0	0.1	0.00	0.00, 37.66	0	0.2	0.00	0.00, 15.85	0	0.3	0.00	0.00, 13.63	0	0.3	0.00	0.00, 11.38
Hypertension (401–405)	0	0.2	0.00	0.00, 15.68	0	0.5	0.00	0.00, 7.75	0	0.5	0.00	0.00, 7.87	0	0.4	0.00	0.00, 8.29
Heart disease (393–398, 410–429)	0	1.1	0.00	0.00, 3.47	1	2.2	0.46	0.01, 2.55	6	3.3	1.84	0.68, 4.01	4	4.2	0.95	0.26, 2.42
Cerebrovascular disease (430–438)	1	2.0	0.50	0.01, 2.76	2	3.9	0.52	0.06, 1.87	4	4.5	0.89	0.24, 2.28	4	4.3	0.93	0.25, 2.38
Hepatic disease (570–573)	0	0.2	0.00	0.00, 22.40	0	0.3	0.00	0.00, 12.54	2	0.4	5.45	0.66, 19.69	2	0.4	4.62	0.56, 16.67
	20–24 (1988–1992)				25–29 (1993–1997)				30–34 (1998–2002)				35–39 (2003–2007)			
	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval	Observed, no.	Expected, no.	Standardized Mortality Ratio	95% Confidence Interval
All causes (001–999)	28	23.7	1.18	0.78, 1.71	32	25.8	1.24	0.85, 1.75	32	28.3	1.13	0.77, 1.59	24	29.6	0.81	0.52, 1.21
All cancers (140–208)	5	6.1	0.82	0.27, 1.91	7	7.3	0.97	0.39, 1.99	8	8.3	0.97	0.42, 1.90	5	8.1	0.62	0.20, 1.44
Stomach (151)	2	1.2	1.65	0.20, 5.94	0	1.2	0.00	0.00, 2.96	0	1.3	0.00	0.00, 2.94	0	1.1	0.00	0.00, 3.35
Rectum (154)	0	0.3	0.00	0.00, 14.37	0	0.3	0.00	0.00, 12.79	1	0.3	3.06	0.08, 17.06	0	0.3	0.00	0.00, 11.83
Liver (155)	1	0.5	2.13	0.05, 11.88	0	0.7	0.00	0.00, 5.49	3	0.8	3.76	0.78, 11.00	1	0.7	1.34	0.03, 7.44
Pancreas (157)	0	0.4	0.00	0.00, 8.84	2	0.5	4.01	0.49, 14.49	1	0.6	1.58	0.04, 8.80	0	0.7	0.00	0.00, 5.38

Lung (162)	1	0.7	1.49	0.04, 8.31	1	0.9	1.15	0.03, 6.42	0	1.1	0.00	0.00, 3.50	1	1.1	0.93	0.02, 5.19
Breast (174)	0	0.4	0.00	0.00, 8.55	1	0.6	1.81	0.05, 10.09	1	0.6	1.56	0.04, 8.71	0	0.6	0.00	0.00, 5.84
Uterus (179–182)	0	0.3	0.00	0.00, 11.15	2	0.3	5.78	0.70, 20.88	0	0.4	0.00	0.00, 10.04	0	0.3	0.00	0.00, 11.32
Leukemia (204–208)	0	0.2	0.00	0.00, 22.83	0	0.2	0.00	0.00, 22.11	0	0.2	0.00	0.00, 19.07	0	0.2	0.00	0.00, 20.57
Diabetes mellitus (250)	1	0.3	3.04	0.08, 16.92	0	0.5	0.00	0.00, 7.70	0	0.4	0.00	0.00, 9.10	1	0.4	2.44	0.06, 13.60
Hypertension (401–405)	1	0.3	2.94	0.07, 16.39	0	0.3	0.00	0.00, 13.44	0	0.2	0.00	0.00, 16.21	0	0.2	0.00	0.00, 17.92
Heart disease (393–398, 410–429)	8	5.1	1.57	0.68, 3.09	10	4.2	2.40	1.15, 4.41	4	4.8	0.84	0.23, 2.16	1	5.3	0.19	0.00, 1.06
Cerebrovascular disease (430–438)	5	4.0	1.26	0.41, 2.94	4	4.6	0.87	0.24, 2.24	6	4.4	1.36	0.50, 2.95	6	4.1	1.46	0.54, 3.17
Hepatic disease (570–573)	0	0.5	0.00	0.00, 8.03	0	0.4	0.00	0.00, 9.60	0	0.4	0.00	0.00, 10.15	0	0.3	0.00	0.00, 10.67

Abbreviation: ICD-9, *International Classification of Diseases*, Ninth Revision.

main isomer was 1,2,3,4,7,8-hexa-CDF (51). Fourteen years after exposure, the blood concentration of 2,3,4,7,8-penta-CDF was 5 times higher in Yusho patients than in those with Yucheng (52). These results are in support of the suggestions that chemicals such as PCDFs could have played an important role in the etiology of Yusho and Yucheng cases. In addition, there were important differences in the type and levels of furans present in the Yusho and Yucheng incidents, and these may be the reason for the different results observed in the 2 studies.

We are confident that the study was not affected by major selection effects; vital status ascertainment was nearly complete. However, our study has several methodological limitations. The most important one is that we determined the person-years at risk for each Yusho case beginning from the patient's official registration date. This is because Yusho patients were designated according to clinical symptoms and eventually diagnosed between 1968 and 1972. In 1972, the blood concentration of PCB was included in the diagnostic criteria (53). In addition, the blood concentration of polychlorinated quaterphenyl was also included in the diagnostic criteria in 1981 (53). These unavoidable designation procedures may have caused us to miss potentially affected patients who died prior to the official registration period.

In conclusion, we have updated the follow-up data and reevaluated the effect of PCBs and PCDFs on major causes of mortality. The revised data demonstrate that the risk of mortality due to all types of cancer, liver cancer, and lung cancer among males significantly increased in comparison with that in the general population. In addition, the standardized mortality ratios for all cancers, liver cancer, and lung cancer among males tended to decrease over time. We also confirmed previously observed increases in the rates of other cancer- and noncancer-related deaths, although we are unable to fully interpret these data for several reasons, including the possibility of false-positive associations due to the large number of comparisons made. Our results suggest that the carcinogenicity of PCBs and PCDFs must be taken into account when evaluating mortality risk. Our findings highlight the importance of further investigating the carcinogenic effects associated with exposure to PCBs and PCDFs.

ACKNOWLEDGMENTS

Author affiliations: Department of Information Science, Fukuoka Institute of Health and Environmental Sciences, Dazaifu-shi, Fukuoka, Japan (Daisuke Onozuka); Fukuoka Institute of Health and Environmental Sciences, Dazaifu-shi, Fukuoka, Japan (Takesumi Yoshimura); Department of Clinical Epidemiology, University of Occupational and Environmental Health, Japan, Yahata-nishi-ku, Kitakyushu-shi, Fukuoka, Japan (Takesumi Yoshimura, Satoshi Kaneko); Institute of Tropical Medicine, Nagasaki University, Nagasaki-shi, Nagasaki, Japan (Satoshi Kaneko); and Department of Dermatology, Kyushu University Graduate School of Medicine, Higashi-ku, Fukuoka-shi, Fukuoka, Japan (Masutaka Furue).

This work was supported by a Grant-in-Aid for Research on Environmental Health from the Ministry of Health, Labour, and Welfare, Japan.

The authors express their sincere appreciation to Yoshie Yamashiro and Dr. Masato Ikeda, who greatly contributed to the management of the cohort data for the Yusho patients. The authors are also grateful to all staff of the municipalities, who contributed to the collection of follow-up data.

Conflict of interest: none declared.

REFERENCES

1. Kuratsune M, Yoshimura T, Matsuzaka J, et al. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. *Environ Health Perspect*. 1972;1(Apr):119–128.
2. Hsu ST, Ma CI, Hsu SK, et al. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year followup. *Environ Health Perspect*. 1985;59(Feb):5–10.
3. Sinks T, Steele G, Smith AB, et al. Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol*. 1992; 136(4):389–398.
4. Kimbrough RD, Doemland ML, Mandel JS. A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. *J Occup Environ Med*. 2003;45(3): 271–282.
5. Ruder AM, Hein MJ, Nilsen N, et al. Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. *Environ Health Perspect*. 2006;114(1):18–23.
6. Bertazzi PA, Riboldi L, Pesatori A, et al. Cancer mortality of capacitor manufacturing workers. *Am J Ind Med*. 1987;11(2): 165–176.
7. Tironi A, Pesatori A, Consonni D, et al. The mortality of female workers exposed to PCBs. *Epidemiol Prev*. 1996; 20(2-3):200–202.
8. Prince MM, Ruder AM, Hein MJ, et al. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Environ Health Perspect*. 2006;114(10):1508–1514.
9. Brown DP, Jones M. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. *Arch Environ Health*. 1981;36(3):120–129.
10. Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. *Arch Environ Health*. 1987;42(6): 333–339.
11. Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Am J Ind Med*. 1986; 10(4):341–344.
12. Gustavsson P, Hogstedt C. A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Am J Ind Med*. 1997;32(3):234–239.
13. Charles LE, Loomis D, Shy CM, et al. Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. *Am J Epidemiol*. 2003;157(8): 683–691.
14. Fingerhut MA, Halperin WE, Marlow DA, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *N Engl J Med*. 1991;324(4):212–218.
15. Steenland K, Piacitelli L, Deddens J, et al. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J Natl Cancer Inst*. 1999;91(9):779–786.
16. Flesch-Janys D, Steindorf K, Gurn P, et al. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ Health Perspect*. 1998;106(suppl 2):655–662.
17. Hooiveld M, Heederik DJ, Kogevinas M, et al. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am J Epidemiol*. 1998;147(9):891–901.
18. Ott MG, Zober A. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. *Occup Environ Med*. 1996;53(9): 606–612.
19. Ketchum NS, Michalek JE. Postservice mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results. *Mil Med*. 2005; 170(5):406–413.
20. Saracci R, Kogevinas M, Bertazzi PA, et al. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet*. 1991;338(8774):1027–1032.
21. Bertazzi PA, Consonni D, Bachetti S, et al. Health effects of dioxin exposure: a 20-year mortality study. *Am J Epidemiol*. 2001;153(11):1031–1044.
22. Consonni D, Pesatori AC, Zocchetti C, et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. *Am J Epidemiol*. 2008;167(7):847–858.
23. Masuda Y. Causal agents of Yusho. In: Kuratsune M, Yoshimura H, Hori Y, et al, eds. *YUSHO: A Human Disaster Caused by PCBs and Related Compounds*. Fukuoka, Japan: Kyushu University Press; 1996:47–80.
24. Ohgami T, Nonaka S, Yoshida H, et al. PCB and PCQ concentrations of the blood and subcutaneous tissue in patients with PCB poisoning (Yusho). *Fukuoka Igaku Zasshi*. 1987; 78(5):337–342.
25. Masuda Y, Kuroki H, Haraguchi K, et al. The condition of PCBs and PCDFs in the blood of Yusho patients 20 years after the onset. *Fukuoka Igaku Zasshi*. 1997;88(5):149–156.
26. Ikeda M, Kuratsune M, Nakamura Y, et al. A cohort study on mortality of Yusho patients—a preliminary report. *Fukuoka Igaku Zasshi*. 1987;78(5):297–300.
27. Ikeda M, Yoshimura T. Survival of patients. In: Kuratsune M, Yoshimura H, Hori Y, et al, eds. *YUSHO: A Human Disaster Caused by PCBs and Related Compounds*. Fukuoka, Japan: Kyushu University Press; 1996:315–323.
28. Hsieh SF, Yen YY, Lan SJ, et al. A cohort study on mortality and exposure to polychlorinated biphenyls. *Arch Environ Health*. 1996;51(6):417–424.
29. Tsai PC, Ko YC, Huang W, et al. Increased liver and lupus mortalities in 24-year follow-up of the Taiwanese people highly exposed to polychlorinated biphenyls and dibenzofurans. *Sci Total Environ*. 2007;374(2-3):216–222.
30. Iwasaki T, Miyake T, Ohshima S, et al. A method for identifying underlying causes of death in epidemiological study. *J Epidemiol*. 2000;10(6):362–365.
31. Breslow NE, Day NE. *Statistical Methods in Cancer Research.* Vol II. *The Design and Analysis of Cohort Studies*. Lyon, France: International Agency for Research on Cancer; 1987. (IARC scientific publication no. 82.).
32. Kociba RJ, Keyes DG, Beyer JE, et al. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rats. *Toxicol Appl Pharmacol*. 1978;46(2): 279–303.
33. 't Mannetje A, McLean D, Cheng S, et al. Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. *Occup Environ Med*. 2005;62(1):34–40.

34. Warner M, Eskenazi B, Mocarelli P, et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect*. 2002;110(7):625–628.
35. Eskenazi B, Warner M, Samuels S, et al. Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. *Am J Epidemiol*. 2007;166(1):79–87.
36. Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monogr Eval Carcinog Risks Hum*. 1997;69:1–631.
37. Eskenazi B, Mocarelli P, Warner M, et al. Serum dioxin concentrations and endometriosis: a cohort study in Seveso, Italy. *Environ Health Perspect*. 2002;110(7):629–634.
38. Bueno de Mesquita HB, Doornbos G, Van der Kuip DA, et al. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in the Netherlands. *Am J Ind Med*. 1993;23(2):289–300.
39. Nowell PC. Origins of human leukemia: an overview. In: Brugge J, Curran T, Harlow E, et al, eds. *Origins of Human Cancer: A Comprehensive Review*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 1991.
40. Scélo G, Boffetta P, Autier P, et al. Associations between ocular melanoma and other primary cancers: an international population-based study. *Int J Cancer*. 2007;120(1):152–159.
41. World Health Organization. *Mortality and Burden of Disease*. Geneva, Switzerland: WHO Statistical Information System (WHOSIS); 2002. (http://www.who.int/whosis/en/).
42. Japanese Red Cross Society. *Kenkyu-houkoku-syo, 1993–1996*. Tokyo, Japan: Japanese Red Cross Society; 1996.
43. Oomi K, Yamamoto A. *Report on Changes in Vital Statistics of Japan 1995; Effects From Implementation of ICD 10 and Revision of Form of Death Certificate.* WHO/HST/ICD/97/54 Meeting of Heads of WHO Collaborating Centers for the Classification of Diseases. Copenhagen, Denmark: World Health Organization; 1997.
44. Hirako T, Shirayoshi K, Nakada T, et al. *Change in Mortality Statistics by Revision of Form of Death Certificate and Implementation of ICD-10 in Japan.* WHO/GPE/ICD/C/99.54 Meeting of Heads of WHO Collaborating Centres for the Classification of Diseases. Cardiff, Wales: World Health Organization; 1999.
45. Naruse Y, Nakagawa H, Yamagami T, et al. Ischaemic heart disease deaths in a Japanese rural area evaluated by clinical records. *J Epidemiol*. 1997;7(2):71–76.
46. Satto I, Ozawa H, Aono H, et al. Re-evaluation of heart disease deaths on death certificates and trends for ischaemic heart disease mortality during the last five years in Oita city. *Nippon Koshu Eisei Zasshi*. 1997;44(4):292–303.
47. Toshima H. Coronary artery disease trends in Japan. *Jpn Circ J*. 1994;58(3):166–172.
48. Ikeda M. Comparison of clinical picture between Yusho/Yucheng cases and occupational PCB poisoning cases. *Chemosphere*. 1996;32(3):559–566.
49. Masuda Y, Kuratsune M. Toxic compounds in the rice oil which caused Yusho. (In Japanese). *Fukuoka Igaku Zasshi*. 1979;70(4):229–237.
50. Van den Berg M, Birnbaum L, Bosveld AT, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ Health Perspect*. 1998;106(12):775–792.
51. Masuda Y, Kuroki H, Haraguchi K, et al. PCB and PCDF congeners in the blood and tissues of Yusho and Yu-cheng patients. *Environ Health Perspect*. 1985;59(Feb):53–58.
52. Masuda Y, Haraguchi K, Kuroki H, et al. Change of PCDF and PCB concentrations in the blood of Yucheng and Yusho patients for 25 years. *Fukuoka Igaku Zasshi*. 1995;86(5):178–183.
53. Kuratsune M, Yoshimura H, Hori Y, et al. *YUSHO: A Human Disaster Caused by PCBs and Related Compounds*. Fukuoka, Japan: Kyushu University Press; 1996.