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A Cohort Study on Mortality and Exposure to Polychlorinated Biphenyls

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ABSTRACT. In 1979, an outbreak of food poisoning ("Yu-Cheng") occurred in Central Taiwan, ROC, involving more than 2 000 people. The event was caused by ingestion of rice oil contaminated with polychlorinated derivatives of biphenyls, dibenzofurans, and quaterphenyls. A retrospective cohort study on mortality was undertaken, and possible long-term health effects in the affected individuals were studied. The mortality experience of 1 940 victims (929 males, 1 011 females) between 1980 and 1991 was compared with the expected numbers, which were calculated from national and local mortality rates. By the end of 1991, 102 deaths were identified, thus producing a standardized mortality ratio (SMR) of overall mortality of 0.99 for males and 1.34 for females. Total cancer mortality was lower than in each comparison group. Mortality from liver diseases was elevated significantly (SMR = 3.22), especially during the first 3 y after the food-poisoning event (SMR = 10.76). Increased clinical severity of polychlorinated biphenyl intoxication was associated with increased mortality from all causes and from liver diseases. In summary, there was a positive association between mortality and intoxication dose, and severe polychlorinated biphenyl poisoning acutely affected mainly the liver. A continued follow-up of this cohort would be valuable in the study of long-term health effects of polychlorinated biphenyl poisoning.

IN 1979, a food poisoning incident ("Yu-Cheng") occurred in Taichung, Changhua, and Miaoli counties in central Taiwan, Republic of China.[1] Approximately 2 000 residents inadvertently ingested rice oil contaminated with polychlorinated biphenyls (PCBs), which were used as a heat-transfer medium in a rice oil manufacturing process. The poisoned residents had common symptoms of acneform eruptions, follicular accentuation, pigmentation of skin and nails, hypersecretion of the meibomian gland, peripheral neuropathy, and abdominal pain. A similar outbreak, which also resulted from PCB-contaminated rice oil, occurred 11 y earlier among approximately 1 800 persons in western Japan who were affected. These individuals showed similar clinical manifestations, which were described collectively as "Yusho" (i.e., Japanese term for oil disease).[2] Both incidents were

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caused by the ingestion of rice oil contaminated with PCBs and by the products of PCB thermal degradation, including polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs).[3-5]

Skin and ocular manifestations were the most dominant symptoms in both food poisoning populations, and these symptoms are often used as the criteria to grade clinical severity of patients with PCB poisoning.[1,6] Acute liver toxicity was a major problem for victims of PCB poisoning. Hepatomegaly and elevations of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, and triglycerides were seen in many Yusho and Yu-Cheng patients.[7,8] Mild abnormalities in liver function have been reported in PCB-exposed occupational cohorts, but overt clinical liver disease been reported only rarely.[9-13]

Evidence of carcinogenic effects from PCBs in different species of animals has been reported in several studies. The focus of most of these studies were focused on liver carcinogenesis and on the effects of PCBs to either induce cancer directly or to modulate the response to other liver carcinogens. In 1978, the International Agency for Research on Cancer (IARC) deemed that sufficient evidence existed to conclude that PCBs were carcinogenic to animals.[14] Until the Yusho incident in 1968, no human effects from PCB exposure had been reported. Currently, the evidence in support of PCB carcinogenicity in humans is still considered inadequate by IARC.[15] In several occupational cohort studies, associations have been found between PCB exposure and excess risk of melanoma and malignant neoplasm of the lung, gastrointestinal tract, liver, and hematopoietic tissue[16-19]; in other studies, however, no increase in cancer mortality has been reported.[12,20,21] Recently, an analysis of the cohort of Yusho patients in Japan[2] revealed an increased mortality for both males and females from liver cancer, chronic liver diseases, and cirrhosis.[22] Mortality from all malignant neoplasms and from lung cancer also increased among males. A decreased mortality from cerebrovascular diseases was observed for both males and

During the 12 y that followed the Yu-Cheng event, no investigation was conducted io which the mortality experience of the PCB-exposed patients was investigated. In view of the demonstrated toxic effects of PCBs on animals, as well as the increased overall cancer mortality among Yusho individuals, the opportunity now exists for assessment of the long-term health effects experienced by Yu-Cheng patients. We therefore conducted a retrospective cohort mortality study among exposed individuals to quantify the chronic heal& effects of PCB intoxication. We specifically questioned whether individuals who ingested PCB-contaminated rice oil had experienced any increase in cause-specific mortality

Material and Method

Since 1979—after the Yu-Cheng outbreak—the Health Department in Taiwan investigated and registered every PCB-exposed case. Two groups of persons were included in the registration: (1) persons with clinical symptoms who visited local hospitals, and (2) asymptomatic persons who reported that they ingested the contaminated rice oil. The second group had used the rice oil produced from the factory that produced PCB-contaminated rice oil. The study cohort was based on all cases registered through 1979; a total of 2 038 cases (976 males and 1 062 females] was identified. Ninety-nine cases were excluded because of either missing citizen identification numbers or failure to ascertain vital status during follow-up. In this study, therefore, I 940 cases 1929 males and 1 011 females) were included (i.e., > 95% of all registered cases).

In this study, we examined the 12-y (i.e., 1980–1991) mortality experience of PCB-intoxicated persons. Ascertainment of vital status as of December 31, 1991, comprised several steps. During the period from 1980 to 1984, demographic information for the study subjects was compared manually with death records from local health bureaus. A copy of the death certificate for each deceased person was then obtained. Since 1985, citizenship identification numbers have been available in the national death registration computerized data, and this enabled search of the deceased cases via computer matching. Tu avoid the loss of death cases and to confirm the death certification data, we also reviewed the death certification files of PCB victims from local health bureaus in Taichung, Changhua, and Miaoli counties, where the outbreak occurred. During the study (i.e., in 1981), the death classification system was revised, and the Ninth Revision of the International Classification of Diseases (ICD-9) was used. A trained physician reviewed all death certificates for deaths that occurred in 1980 and, using the ICD-9, recorded the underlying cause of death for each.

Person-years of the study subjects were accumulated from the beginning of the follow-up (January 1, 1980) to the date of dead, or to the study termination date (December 31, 1991), whichever occurred first. Expected numbers of deaths for selected causes of death were computed by multiplying the average age- and sex-specific death rates of Taiwan (the comparison population) by the person-years at risk in the corresponding strata. Mortality excesses and deficits were expressed as standardized mortality ratios (SMRs).[23] The SMR is the number of observed deaths in the study cohort divided by the number of deaths that would have been expected if the death rates for a comparison papulation were in effect. To help adjust for geographic variations in mortality and for the potential influence of confounding factors, we computed a second set of expected numbers of deaths, using mortality rates for the resident population of the counties in which the poisoning incidents occurred. The 95% confidence interval (95% CI) for each SMR was calculated, and its deviation from 1 was tested, assuming a Poisson distribution for the observed deaths, using a two-sided test of significance?'

We used Poisson regression analysis to asses the independent effects of sex, age, level of PCB intoxication, and time period after PCB exposure among the study subjects.[25] Adjusted rate ratios and their 95% CIs for the above-mentioned variables were calculated with STATA

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software.[26] Given that clinical severity was related closely to total amount of rice oil consumed and to blood PCB concentration,[27] and given that tests for detecting PCB concentration in blood of an individual were not standardized and that the results often varied according to the amount of time that followed PCB intake, we used clinical severity at the PCB intoxication index to grade poisoned cases (Table 1).[1,6] Cases that were not diagnosed by a physician are not shown in Table 1; a grade of "unknown" was assigned to this group, which included self-reported asymptomatic cases and the few subjects who died early in the outbreak. Owing to a small number of cases—and assuming homogenesis within each risk set[25]—we combined clinical severity grade 0 and unknown (grade I and II, grade III and IV) to form three severity groups in the Poisson regression model.

Results

A total of 1 940 individuals, including 929 males and 1 011 females, who met the cohort criteria were included in the analysis. The average age at the beginning of the study was 27 y (males = 27.4 y, females = 26.7 y). More than one-half of the cohort members were younger than 30 y of age, whereas the mean age of dead cases in the Yu-Cheng incident was 50 y (males = 46 y, females = 54 y); the mean age at death was 55 y (males = 51, females = 60 [Table 2]). The total number of person-years of observations was 22 688, and the subjects were followed for an average of 11.7 y.

Observed deaths, SMRs, and 95% confidence intervals for selected causes, using the general Taiwan population as the comparison population, are shown in Table 3. The overall mortality experience of this cohort was slightly higher than that of the general population (SMR = 1.12, 95% CI = 0.93–1.36). Males had a similar mortality experience (SMR = 0.99, 95% CI = 0.76–1.29), whereas females had a less *favorable* experience (SMR = 1.34, 95% CI = 1.01–1.78). In both males and females, mortality from all cancer was substantially lower than the *general* population. There were 11 deaths from cancer in the total study cohort, and the age-sex adjusted mortality rate was lower than the Taiwan experience (SMR = 0.58, 95% CI = 0.29–1.04). Mortality rates from cirrhosis of the liver were increased in both sexes, as were the rates for other liver diseases (cirrhosis: SMR = 2.79, 95% CI = 1.35–5.00; other liver diseases: SMR = 5.40, 95% CI = 1.47–13.82). There was a threefold increased mortality from ill-defined conditions. (Table 3). Mortality experience, by calendar time period, is shown in Table 4. Overall mortality (SMR = 1.52, 95% CI = 1.01–2.21) and mortality from liver diseases (SMR = 10.76, 95% CI = 5.37–19.26) were increased significantly during the first 3 y.

Analyses were also performed, using as the second comparison the mortality rates for the resident population of the counties in which the poisoning incidents occurred. The SMRs were slightly lower when the focal population was used as the comparison, compared with the national population (Table 5). The patterns of excesses and deficits, however, were not altered substantially. Observed deaths, SMRs, and their 95% confidence intervals for site-specific cancer, using either the general Taiwan population or residents of the local counties as the comparison population, are shown in Table 6. Mortality for nasopharynx cancer, small-intestine cancer, Hodgkin's disease, and unspecified leukemia in males, as well as mortality for liver and intrahepatic bile ducts cancer and bone cancer in females, were higher than expected. However, given that the number of cases was small

Table 1.—Criteria of Grading of Clinical Severity for Patients with PCB Poisoning

Grade	Main criteria	Reference criteria
0	Abnormal blood level of PCBs without clinical manifestations.	
I	Increased cheese-like discharge from Meibomian gland; pigmentation of nails.	Increasing sweating; dry skin; pigmentation of lips, gingiva, and mucous membranes of oral cavity.
II	Grade I, plus comedo.	Hair follicle keratosis on the extensor side of extremity joints.
III	Grade II, plus acneform eruption; cyst formation of sebaceous gland in genital area; and evidence of follicular opening at neck and upper chest.	Swelling of eye lids and swelling and pain at joints.
IV	Enlarged and elevated follicular opening all over the body and extensive distribution of acneform eruptions.	Swelling of face and limbs; extensive distribution of acne, with purulent infection.

Source: Goto M, Higuchi K. The symptomatology of Yusho (chlorobiphenyls poisoning) in dermatology. Fukuoka Acta Med 1969; 60: 409–31.

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Table 2.—Age and Sex Distribution of Study Cohort

Age*	Males			Females			Total		
	No. subjects	Person-years	No. deaths	No. subjects	Person-years	No. deaths	No. subjects	person-years	No. deaths
< 10	142	622.0	1	101	432.0	2	243	1 054.0	3
10–19	261	2 460.0	9	317	2 226.0	6	578	4 686.0	15
20–29	153	2 435.5	4	259	3 877.0	1	412	63125	5
30–39	132	1831.5	6	104	2 086.5	1	236	3 918.0	7
40–49	104	1 350.5	4	109	1 313.5	4	213	2 664.0	8
≥ 50	137	2 126.0	31	121	1 927.5	33	258	40535	64
Total	929	10825.5	55	1 011	11 862.5	47	1 940	22 688.0	102

*Age at the beginning of the study (1980), or age at death for deceased cases.

Table 3.—Standardized Mortality Ratios for Selected Causes of Death for Food-Poisoned Patients, with Taiwan as a Comparison Population, 1980–1991

Causes of death (ICD-9)	Males			Females			Total		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All causes (000–999)	55	0.99	0.76–1.29	47	134	1.01–1.78	102	1.12	0.93–1.36
All cancers (140–209)	8	0.69	0.30–1.36	3	0.4	0.08–1.18	11	0.58	0.29–1.04
Cirrhosis of liver (571)	8	2.67	1.15–5.26	3	3.15	0.65–9.21	11	2.79	1.39–5.00
Disease of liver, excluding cirrhosis (570, 572, 573)	1	1.88	0.05–10.50	3	14.28	2.94–41.68	4	5.4	1.47–13.82
Cerebrovascular disease (430–438)	5	0.65	0.21–1.52	4	0.65	0.18–1.65	9	0.65	0.30–1.23
Ischemic heart disease (410–414)	4	1.99	0.54–5.09	1	0.83	0.02–4.63	5	1.55	0.50–3.62
Other forms of heart disease (420–429)	4	1.51	0.41–3.87	2	0.98	0.12–3.53	6	1.28	0.47–2.79
Accidents (E800–E949)	8	0.74	0.32–1.46	5	1.36	0.44–3.18	13	0.9	0.48–1.53
Ill-defined diseases (780–799)	7	3.43	1.38–7.07	5	3.42	1.05–7.54	12	3.35	1.73–5.86

Notes: ICD = international classification of diseases (ninth revision), OBS = observation number, SMR = standardized mortality ratio, and CI = confidence interval.

(with the exception of Hodgkin's disease). *the excess* was not statistically significant.

The fitted Poisson regression models for factors associated with overall mortality, liver diseases, and all cancer mortality among Yu-Cheng subjects are shown in Table 7. After adjusting *effects of other* factors, we found that age was associated significantly with overall mortality, mortality from cancer, and mortality from liver diseases. After adjusting for *age*, sex, and time period since PCB exposure, we *determined* that an increase in clinical severity of PCB *intoxication* was associated with increased mortality from all causes and from liver diseases. Compared with asymptomatic subjects, *cohort* members with *the* most severe clinical grades (III and IV) had significantly higher mortality from all causes (adjusted mortality rate ratio = 1.85) and from liver diseases (adjusted rate ratio = 5.38). *Mortality* from liver diseases *during the first 3 y* after PCB exposure was more than 8 times higher than that in the subsequent 9 y.

Discussion

We examined the mortality experience of a *cohort of* 1 940 Yu-Cheng patients who accidentally consumed cooking oil contaminated by a mixture of polychlorinated aromatics—predominately PCBs. The study *subjects* were followed for 12 y after the incident occurred in *1979*. Within the *first* year of the outbreak, most of these victims became ill with a systemic form of chloracne, which consisted of acneform eruptions, hyperpigmentation, peripheral neuropathy, abdominal pain, *and* deformation of the nails. Many individuals still *suffered* from the effects of the intoxication after more than 2 y. Detectable levels of *these* chemicals in *the* blood can exist up to 4 y after the first exposure. Thermal degradation by-products of PCBs (e.g., PCDFs, PCQs) ingested by Yu-Cheng victim could have been stored in body fat, thus preventing their rapid metabolization or excretion. To *date*, the chronic health effects of PCB exposure of these patients have not been examined in a study, although a descriptive 4-y follow-up study was reported.[1] By the end of 1991, 102 deaths had been identified, accounting for 5.2% of the total study population. In *our study*, we found a sharp increase in overall mortality during the first 3 y (age-and sex-standardized SMR = 1.52). *At* the end of 12 y, however, the survival experience of Yu-Cheng patients was not much different from that of the general population. An

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increase in mortality from all cancers was not apparent *in the* study cohort; in fact, total cancer mortality was decreased. Although it has been reported that PCBs can cause hepatocellular carcinoma in rats,[9] there was no increase in liver cancer mortality in this *cohort.* However, mortality from cirrhosis of the liver and other nonmalignant liver diseases among Yu-cheng patients was increased significantly; the age- and sex-adjusted mortality was almost threefold higher (SMR = 3.22) than the general population. This finding clearly indicated a strong hepatic toxicity of PCBs and their thermal degradation products. A is likely, however, that *there* might have been liver cancer cases among the cases with liver diseases; *perhaps* there was a lack of diagnostic workup or a coexistence of liver cirrhosis and liver cancer.

In addition to the recently reported increased mortality[1] from liver cancer, chronic liver diseases, and cirrhosis, initial studies of Yusho patients revealed abnormalities in routine liver function *tests* in several cases.[8] Similarly, there was a high prevalence of abnormal liver function tests among Yu-Cheng patients.[1] Although there was ample evidence of hepatic effects from PCBs in experimental animals, chronic human hepatotoxicity from PCBs was *not* remarkable in occupational *cohort* studies.[10–13] The possible explanations for the discrepancy are several. The routes of exposure and absorption in occupational groups were mainly dermal or by inhalation. In this *study,* patients *ingested* PCBs through *the gas*trointestinal tract, which required hepatic metabolism. Composition of exposure may also account for the dis-

Table 4.—Standardized Mortality Ratios for Overall Cause, Cancer, and Liver Diseases, by Calendar Year, with Taiwan as a Comparison Population

	Males			Females			Total		
Calendar year	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
Overall cause									
1980–1982	16	1.42	0.81–2.29	12	1.69	0.87–2.96	28	1.52	1.01–2.21
1983–1988	20	0.72	0.44–1.11	22	1.25	0.78–1.88	42	0.92	0.68–1.25
1989–1991	19	1.14	0.69–1.78	13	1.26	0.67–2.15	32	1.19	0.84–1.68
Total	55	0.99	0.76–1.29	47	1.34	1.01–1.78	102	1.12	0.93–1.36
Total cancer									
1980–1982	1	0.45	0.01–2.51	1	0.66	0.02–3.69	2	0.54	0.06–1.94
1983–1988	3	0.51	0.11–1.50	1	0.27	0.01–1.48	4	0.42	0.11–1.08
1989–1991	4	1.13	0.31–2.90	1	0.46	0.01–2.59	5	0.88	0.28–2.05
Total	8	0.69	0.30–1.36	3	0.40	0.08–1.18	11	0.58	0.29–1.04
Liver diseases									
1980–1982	7	8.95	3.59–18.43	4	16.66	4.53–42.66	11	10.76	5.37–19.26
1983–1988	1	0.57	0.01–3.19	2	3.49	0.42–12.58	3	1.29	0.27–3.78
1989–1991	1	1.02	0.03–5.70	0	—	—	1	0.76	0.02–4.21
Total	9	2.57	1.18–4.88	6	5.17	1.90–11.26	15	3.22	1.80–5.31

Notes: OBS = observation number, SMR = standardized mortality ratio, and CI = confidence interval.

Table 5.—Standardized Mortality Ratios for Selected Causes of Death for Food-Poisoned Patients, with Local Populations as a Comparison Population, 1980–1991

	Males			Females			Total		
Causes of death (ICD-9)	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All causes (000–999)	55	0.94	0.73–1.23	47	1.27	0.96–1.69	102	1.07	0.87–1.28
All cancers (140–209)	8	0.66	0.28–1.29	3	0.40	0.08–1.18	11	0.56	0.28–1.00
Cirrhosis of liver (571)	8	2.39	1.03–4.72	3	2.73	0.56–7.97	71	2.48	1.23–4.43
Disease of liver, excluding cirrhosis (570, 572, 573)	1	2.14	0.05–11.94	3	15.82	3.26–46.20	4	6.10	1.66–15.61
Cerebrovascular disease (430–438)	5	0.61	0.20–1.42	4	0.61	0.17–1.56	9	0.58	0.27–1.11
Ischemic heart disease (410–414)	4	1.97	0.54–5.04	1	0.78	0.02–4.34	5	1.51	0.49–3.52
Other forms of heart disease (420–429)	4	1.35	0.37–3.46	2	1.00	0.12–3.64	6	1.22	0.45–2.65
Accidents (E800–E949)	8	0.79	0.34–1.55	5	1.32	0.40–2.84	13	0.91	0.48–1.56
Ill-defined diseases (780–799)	7	3.34	1.34–6.89	5	2.81	0.91–6.55	12	3.10	1.60–5.42

Notes: ICD = international classification of diseases (ninth revision), OBS = observation number, SMR = standardized mortality ratio, and CI = confidence interval.

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Table 6.—Standardized Mortality Ratios for Site-Specific Cancer for Food-Poisoned Patients, 1980–1991

Cancer sites (ICD-9)	OBS	Reference mortality: National SMR	National 95% CI	Local SMR	Local 95% CI
Males					
Nasopharynx (147)	1	1.54	0.04–8.61	1.40	0.04–7.82
Stomach (151)	1	0.63	0.02–3.53	0.65	0.02–3.59
Small intestine (152)	1	19.76	0.50–110.06	26.46	0.67–147.40
Liver and intrahepatic bile ducts (155)	1	0.29	0.01–1.62	0.32	0.01–1.80
Trachea, bronchus, and lung (162)	2	0.85	0.10–3.07	0.92	0.11–3.32
Hodgkin's disease (201)	1	61.17	1.55–340.72	86.45	2.19–481.52
Unspecified leukemia (208)	1	7.69	0.19–42.84	8.42	0.21–46.89
Females					
Liver and intrahepatic bile ducts (155)	1	1.08	0.03–6.02	1.23	0.03–6.87
Trachea, bronchus, and lung (162)	1	0.88	0.02–4.91	1.05	0.03–5.84
Bone (170)	1	8.32	0.21–46.38	7.89	0.20–43.94

Notes: ICD = international classification of diseases (ninth revision), OBS = observation number, SMR = standardized mortality ratio, and CI = confidence interval.

crepancy mentioned earlier. The exposure in this cohort may have been to a combination of PCBs, PCDFs, and other related compounds, instead of to PCBs only. These additional compounds evolved from thermal degradation during the processing of rice oil; occupational exposures, however, were limited to PCBs. Dermatological and systemic changes have been noted in experimental studies for which a mixture of PCDFs—similar to the mixture in Yusho oil—was used; however, administration of either PCBs or PCQs alone failed to induce such changes.[26,29] By far the most impressive clinical picture presented by Yu-Cheng patients revealed that, in addition to PCB contaminants, the intoxication resulted from PCQ and PCDF contaminants.[30] This explanation relates to the exposure dose. The acute effects of high exposure induced serious hepatic toxicity—or even hepatic failure—but the chronic effects on the liver that resulted from long-term, low-dose exposure (as occurs in occupational cohorts) appeared to be mild. Fatal liver conditions could only occur after certain levels of PCBs existed in the blood. The average blood PCB concentration at the early stage of the outbreak ranged from 3 ppb to 1 156 ppb; 44% of patients had levels of 5–100 ppb, and 27.6% had PCB levels that exceeded 100 ppb.[31] It should be noted that in this study, 75% of the deaths from liver diseases occurred during the first 3 y after exposure occurred. The mortality of liver diseases during the first 3 y was compared with mortality during the subsequent 9 y, and the adjusted rate ratio was 8.84 (95% CI = 2.80–27.85).

The excess of deaths from liver disease during the early years after PCB intoxication revealed a short latent period for lethal liver diseases. Given the seriousness of the disease it is possible, but unlikely, that bias in certifying cause of death might have accounted for this observation. Mortality from liver cirrhosis and other nonmalignant livw diseases for subjects who were less than 50 y of age and for subjects 50+ y of age was m e than five-fold higher (SMR = 5.62, 95% CI = 2.57–10.681 and approximately twofold higher (SMR = 1.89, 95% CI = 0.69–4.11), respectively, than mortality from livw diseases for the corresponding general population.

The brief latent period was responsible for the low cancer mortality for the total 12-y follow-up period. Nonetheless, mortality during the fast 3 y was substantially higher than that experienced during the first 9 y; however, SMRS for nasopharynx cancer, small-intestine cancer, Hodgkin's disease, unspecified leukemia, and bone cancer were h P than expected. It has been reported in other stu es" that small-intestine cancer, Hodgkin's disease, and unspecified leukemia are associated with PCB exposure; however. only the SMR for Hodgkin's disease was significant. The SMRs for other cancers were not significant; this result might reflect the small number of cases.

ti was noted in some studies that the concentration of PCBs in patients' serum correlated with blood pressure and triglycerides.[9,10] Even though mortality from ischemic hear? disease in males was increased slightly in these studies, we did not find any significant increase in cerebrovascular disease or in ischemic heart disease. It is noteworthy that there was a significant increase in incidence of ill-defined conditions (ICD codes 780–789). Perhaps this finding resulted from a decreased access to better diagnostic work-up. Some cases died from acute liver failure, but underlying causes on death certifications were "died from PCB poisoning." Causes of death for these cases were classified as ill-defined. Although it is impossible to speculate the exact cause if more medical work-up had been performed, the observed increase in liver disease could only be more than what was reported here.

Studies of the association between the amount of PCB exposure and mortality have yielded a variety of results.[19,32] After adjusting for sex, age, and time period after exposure, we noted positive associations between clinically defined exposure severity and mortality from all causes, as well as liver diseases. This positive pattern should be examined further, and a longer period of follow-up should be included.

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Table 7.—Multivariate Adjusted Rate Ratios for Mortality of Food-Poisoned Patients, According to Sex, Age, Clinical Severity, and Calendar Year, by Poisson Regression

Factors	Overall causes			Total cancer			Liver diseases		
	Person-years	Case no.	a_RR (95% CI)	Person-years	Case no.	a_RR (95% CI)	Person-years	Case no.	a_RR (95% CI)
Gender									
Male	10 825.5	55	1.10 (0.75–1.63)	10 848.0	8	2.43 (0.64–9.20)	10 848.5	9	1.46 (0.52–4.11)
Female	11 862.5	47	1.00	11 884.5	3	1.00	11 884.0	6	1.00
Age (y)									
< 55	18 634.5	31	1.00	18 649.5	1	1.00	18 646.5	9	1.00
≥ 50	4 053.5	77	10.74 (7.01–16.44)	4 003.5	10	45.10 (5.73–354.9)	4 086.0	6	3.76 (1.33–10.69)
Clinical severity*									
0, unknown†	9 301.5	41	1.00	9 326.0	4	1.00	9 325.5	3	1.00
I-II	10 442.5	39	1.11 (0.72–1.73)	10 459.5	5	1.62 (0.43–6.04)	10 459.5	7	2.39 (0.62–9.31)
III-IV	2 944.0	22	1.85 (1.10–3.12)	2 947.0	2	1.66 (0.30–9.12)	2 947.5	5	5.38 (1.28–22.56)
Calendar year									
1980–1982	5 782.0	28	1.33 (0.86–2.06)	5 795.0	2	0.84 (0.18–3.91)	5 790.5	11	8.84 (2.80–27.85)
1983–1991	16 906.0	74	1.00	16 937.5	9	1.00	16 942.0	4	1.00

Notes: a_RR = multivariate adjusted rate ratio, CI = confidence interval.
*Grade of clinical severity.
†Asymptomatic cases for whom PCB levels in blood were not determined.

In summary, we found an acute *effect* of high-dose intoxication of PCBs, *mainly* in the liver. The multivariate-adjusted rate ratios for all causes of mortality and for mortality from liver diseases were elevated among those who had more severe clinical symptoms from exposure. Continued follow-up of the disease experience of this *cohort* might provide insight into *the* long-term health effects of PCB intoxication.

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Submitted for publication October 31, 1995; revised; accepted for publication April 24, 1996.

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References

1. Hsu ST, Ma CI, Hsu SK, et al. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year follow-up. Environ Health Perspect 1985; 59:5–10.
2. Kuratsune M, Moritawa Y, Hirohata T, et al. An epidemiological study on "Yusho" or chlorobiphenyls poisoning. Fukuoka Acta Med 1969; 60:513–32.
3. Chen PH, Wong CK, Rappe C, Nygren N. Polychlorinated biphenyls, dibenzofurans and quaterphenyls in toxic rice-bran oil and in the blood and tissues of patients with PCB poisoning (Yu-Cheng) in Taiwan. Environ Health Perspect 1985; 59:59–65.
4. Kashimoto T, Miyata H, Fukushima S, et al. PCBs, PCQs and PCDFs in blood of Yusho and Yu-Cheng patients. Environ Health Perspect 1985; 59:73–78.
5. Miyata H, Fukushima S, Kashimoto T, et al. PCBs, PCQs and PCDFs in tissues of Yusho and Yu-Cheng patients. Environ Health Perspect 1985; 59:67–72.
6. Goto M, Higuchi K. The symptomatology of Yusho (chlorobiphenyls poisoning) in dermatology. Fukuoka Acta Med 1969; 60:409–31.
7. Chang KJ, Chen JS, Huang PC, et al. Studies of patients with polychlorinated biphenyls poisoning. I. Blood analysis of patients. J Formosa Med Assoc 1980; 79:304–13.
8. Higuchi K. PCBs Poisoning and Pollution. New York: Kodansha Ltd. and Academic Press, 1976; p 5.
9. Baker EL, Landrigan PJ, Glueck CJ, et al. Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am J Epidemiol 1980; 112:553–63.
10. Smith AB, Schloemer J, Lowry LK, et al. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. Br J Ind Med 1982; 39:361–69.
11. Fitzgerald EF, Standfast SJ, Youngblood LG, et al. Assessing the health effects of potential exposure to PCBs, dioxins and furans from electrical transformer fires: the Binghamton state office building medical surveillance program. Arch Environ Health 1986; 41:368–76.
12. Fitzgerald EF, Weinstein AL, Youngblood LG, et al. Health effects three years after potential exposure to the toxic contaminants of an electrical transformer fire. Arch Environ Health 1989; 44:214–21.
13. Wolff MS, Fischbein A, Thornton J, et al. Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. Int Arch Occup Environ health 1982; 49:199–208.
14. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol 18. Polychlorinated Biphenyls and Polybrominated Biphenyls. Lyon, France: International Agency for Research on Cancer, 1978; pp 43–103.
15. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Suppl 4. Lyon, France: International Agency for Research on Cancer, 1982; pp 217–19.

May-23-01 02:46pm From- T-467 P.14/15 F-562

16. Bahn AK, Rosenwaike I, Herrmann N, et al. Melanoma after exposure to PCBs. N Engl J Med 1976; 295:450.
17. Bertazzi PA, Riboldi L, Pesatori A, et al. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 1987; 11:165–76.
18. Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. Arch Environ Health 1987; 42:333–39.
19. Sinks T, Steele G, Smith AB, et al. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 1992; 136:389–98.
20. 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; 10:341–44.
21. Brown DP, Jones M. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health 1981; 36:120–29.
22. Ikeda M, Kuratsune M, Nakamura Y, et al. A cohort study on mortality of Yusho patients: a preliminary report. Fukuoka Acta Med 1986; 78:297–300.
23. Tsai SP, Wen CP. A review of methodological issues of the standardized mortality ratio (SMR) in occupational cohort studies. Int J Epidemiol 1986; 15:8–21.
24. Breslow NE, Day NE. Statistical methods in cancer research. Vol 2. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987.
25. Rothman KJ, Modern Epidemiology. Boston, MA: Little, Brown, 1986.
26. State software version 3.00. Santa Monica, CA: Santa Monica Computing Resource Center, 1992.
27. Koda H, Masuuda Y. Relationship between PCBs concentrations or patterns in the blood and clinical symptoms of Yusho patients. Fukuoka Acta Med 1975; 66:624–28.
28. Kunita N, Kashimoto T, Miyata H, et al. Causal agents of Yusho. Am J Ind Med 1984; 5:45–58.
29. Kunita N, Hori S, Obana H, et al. Biological effects of PCBs, PCQs and PCDFs present in the oil causing Yusho and Yu-Cheng. Environ Health Perspect 1985; 59:79–84.
30. Kashimoto T, Miyata H, Kunita S, et al. Role of polychlorinated dibenzofuran in Yosho (PCBs poisoning). Arch Environ Health 1981; 36:321–26.
31. Ko YC, Cheng CT, Jao LT, et al. The blood level of PCBs in the poisoning patients. J Formosa Med Assoc 1981; 80:774–79.
32. U.S. Environmental Protection Agency. Ambient Water Quality Criteria for Polychlorinated Biphenyls (PCBs). Washington, DC: Environmental Protection Agency, 1980.

May-23-01 02:46pm From-
T-467 P.15/15 F-562