

Chloracne, Goiter, Arthritis, and Anemia after Polychlorinated Biphenyl Poisoning: 14-Year Follow-Up of the Taiwan Yucheng Cohort

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In 1979, a mass poisoning involving 2,000 people occurred in central Taiwan from ingestion of cooking oil contaminated by polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs). We studied the prevalence of medical conditions in the exposed individuals and in a neighborhood control group. Starting with a registry of the exposed individuals from 1983, we updated the addresses of exposed individuals and identified a control group matched for age, sex, and neighborhood in 1979. In 1993, individuals 30 years of age or older were interviewed by telephone. We obtained usable information from 795 exposed subjects and 693 control subjects. Lifetime prevalence of chloracne, abnormal nails, hyperkeratosis, skin allergy, goiter, headache, gum pigmentation, and broken teeth were observed more frequently in the PCB/PCDF-exposed men and women. The exposed women reported anemia 2.3 times more frequently than controls. The exposed men reported arthritis and herniated intervertebral disks 4.1 and 2.9 times, respectively, more frequently than controls. There was no difference in reported prevalences of other medical conditions. We conclude that Taiwanese people exposed to high levels of PCBs and PCDFs reported more frequent medical problems, including skin diseases, goiter, anemia, and joint and spine diseases. *Key words:* acneform eruptions, food intoxication, PCBs, polychlorinated biphenyls, skin manifestations, thyroid gland. *Environ Health Perspect* 107:715–719 (1999). [Online 28 July 1999]

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Polychlorinated biphenyls (PCBs) and related compounds are among the most widespread environmental pollutants (1); they have been routinely detected in human tissue samples since the 1960s. In 1979, a mass poisoning occurred in central Taiwan from cooking oil contaminated by heat-degraded PCBs (2). Symptoms included chloracne, hyperpigmentation, and peripheral neuropathy, and the illness was referred to as “Yucheng” (oil disease). By 1983, a registry set up and maintained by the Taiwan Provincial Department of Health included 2,061 subjects (3).

The PCBs involved in Yucheng had been repeatedly heated and cooled and were partially oxidized into polychlorinated dibenzofurans (PCDFs) and other polychlorinated multiple ring structures. Patients used the contaminated cooking oil for an average of 8 months. They were estimated to have consumed about 1 g of PCBs and 3.8 mg of PCDFs (primarily 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF) during that time (4), resulting in median serum PCB concentrations of 40–60 ppb wet weight (ww) and serum PCDF levels of approximately 2.7 ppt ww for pentaCDF and 10.8 ppt ww for hexaCDF. These levels are on the order of 10–20 times higher than background for PCBs and 100–1,000 times higher for pentaCDF and hexaCDF. Some of these chemicals are extremely persistent in human tissue; 14 years after exposure, PCB and PCDF measurement in 56 women from

the cohort showed that total PCBs were still 7-fold higher and PCDF congeners were 50–180 times higher than that of pooled local controls (5).

Individuals poisoned in this incident had excess mortality from nonmalignant liver disease [standardized mortality ratio = 2.7 and 95% confidence interval (CI), 1.3–4.9, based on 10 deaths] at 13 years of follow-up (6), although their overall mortality was not higher than that of the Taiwan general population (standardized mortality ratio 0.8 and CI, 0.7–1.0, based on 83 deaths). To evaluate morbidity in the surviving members of the cohort, we contacted and interviewed them in 1993, 14 years after the exposure had taken place. The Yucheng cohort is quite young: the median age in 1979 was about 20 years. For this investigation we focused on individuals born before 1 January 1963 because we expected this group to have greater morbidity than a younger group.

Subjects and Methods

The Yucheng registry and the mortality follow-up are described elsewhere (6). From 1979 to 1983 the Taiwan Provincial Department of Health registered 2,061 cases based on signs and symptoms of the illness or a history of consumption of the contaminated oil (2). Participation in the registry was voluntary; there was local publicity, and registration provided access to free examinations and medical care. We acquired the registry from the Department of Health in 1991.

Taiwan has local household registration offices in every village, town, and city precinct. The registration offices, among other functions, keep records of deaths, record changes of residence, and maintain forwarding addresses. Using the address listed in the Yucheng registry, we began in 1992 to locate each subject's record at the appropriate registration office; we then traced the subjects through 31 December 1991.

Ideally, a control group would have been identified at the time of the poisoning from the areas where the poisoning occurred and then followed in the same way as the exposed group. No such control group was established at the time. There were no telephone books, city registries, or other archival material that listed the residents in the towns where Yucheng had occurred in 1979 and from which we could draw a contemporaneous control sample. Therefore, we used the 1979 addresses of the registry members as index addresses and attempted to identify the persons who lived nearby in 1979 from the archives of the registration offices. We did this systematically beginning with the higher or lower numbered dwelling at random; we located the record of the current household, and, if that family had not been there in 1979, we worked through the archived records until we found the record of the family who had lived there. We then enumerated the family members and attempted to identify a control subject within the family. Control subjects were required to be of the same sex, within 3 years of age of the index registry member, and could not themselves be in the registry; if a household contained no eligible control subject, the next closest household was tried. We identified three controls for each registry member, and we attempted to contact the control subject living nearest to the

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index address in 1979. We only used one of any triplet set. Exposed and control subjects were interviewed over the telephone with a structured questionnaire. The majority of the interview consisted of asking the participants questions about diseases ever diagnosed by Western-style medical doctors, whether such diseases were treated medically or surgically, and whether they resulted in hospitalization. Accidents and some symptoms and signs were also included in the questionnaire. Interviewers were college graduates from health science fields who were trained by the investigators and were blind to exposure status.

Although the exposed subjects and the eligible controls were matched, some of the exposed subjects had no match among the successfully interviewed controls, and some of the exposed subjects for which there were interviewed controls were not successfully interviewed. Thus, we used chi-square rather than paired techniques to compare the lifetime prevalence of diseases, analyzing each separately.

There were 2,061 subjects in the Yucheng registry (Figure 1). Of these, 70 were offspring of the exposed subjects who were born after 30 June 1978, during or after the incident; because their exposure was primarily transplacental, we excluded them from this study. Of the remaining 1,991 Yucheng subjects, 154 (7%) had either incomplete or wrong addresses recorded by the Yucheng registry and thus could not be traced further. Therefore, a total of 1,837 Yucheng subjects were traced. In 1992, vital status was determined for 1,828 subjects (99.5%); 83 of them died during the follow-up period, leaving 1,745 alive (6). Among the live exposed subjects, 1,144 were born before 1 January 1963. We attempted to find control subjects for these individuals by identifying them from the police records and trying to locate them. We found 1,135 unexposed controls.

We were able to contact 1,003 exposed subjects and 952 control subjects by phone. Although 208 (20.7%) of the Yucheng subjects and 259 (27.2%) of the control subjects refused to be interviewed or gave unusable responses, 795 of the exposed subjects and 693 of the control subjects completed the interview. Those who refused to be interviewed had a similar age and sex distribution as those who participated, were of similar sex ratio as participants, but had attained a slightly higher level of education (7.0 years vs. 6.7 years; $p = 0.05$).

Results

Table 1 summarizes the demographic characteristics of the Yucheng and control subjects. There is no significant difference in

age, sex distribution, education level, and smoking history between the two groups. Skin and oral problems are prominent in the Yucheng group (Table 2): 17% of exposed subjects described acnelike skin lesions compatible with chloracne, as compared to 1.3% of control subjects. Similarly, hyperkeratosis, abnormal nails, gum swelling, gum pigmentation, and broken teeth were all observed more often in the exposed group. Skin allergy, not originally noted to be part of the syndrome, is now the most frequent complaint among the exposed subjects. The prevalence of reported occurrences of chloracne is not significantly different among age groups in Yucheng subjects.

Goiter was reported more often in exposed men and women than in controls, although neither group reported the diagnoses of hyperthyroidism or hypothyroidism more frequently. Headaches were more prevalent in exposed subjects of both sexes than in controls. Exposed women reported being diagnosed for anemia and requiring medication for anemia 2.3 times more frequently than controls. Arthritis was reported 4.1 times more often in exposed men than in control men and medication was required 3.1 times more often. Herniated disks were reported 2.9 times more often in exposed men and required medication 4.1 times more often. When the analysis was limited to matched subjects, 221 pairs of men and

283 pairs of women remained, representing an overall success rate of 53%. The original findings of chloracne, hyperkeratosis, abnormal nails, skin allergy, gum pigmentation, headache, and goiter in both Yucheng men and women; broken teeth and anemia in women; and arthritis and herniated disks in men remained unchanged.

In the Yucheng individuals, the report of chloracne was compared with lifetime prevalence of medical conditions and serum PCB levels determined in 1980–1982 by the Webb-McCall method (2) (Table 3). The occurrence of chloracne was related to other skin findings and PCB levels in 1980–1982 in both Yucheng men and women and to anemia and herniated disks in Yucheng women. When women and men were grouped together, chloracne was found to be associated with headache, herniated disk, and goiter.

Reported prevalences that were not statistically different between the Yucheng group and the control group include cataract, glaucoma, conjunctivitis, otitis media, sinusitis, hearing loss, hypertension, coronary heart disease, lung diseases, renal disease, cystitis, inguinal hernia, hyperuricemia, urethritis, urinary stone, stroke, polyneuritis, epilepsy, Parkinsonism, diabetes mellitus, hyperthyroidism, hypothyroidism, peptic ulcer, liver diseases, gall stone, appendicitis, and accidents.

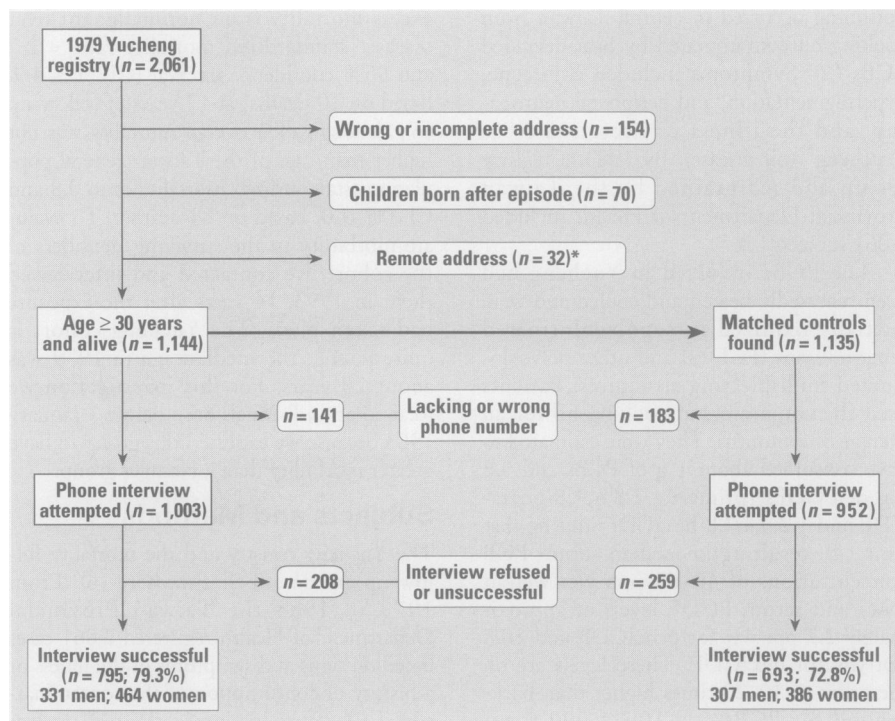


Figure 1. Numbers of individuals in exposed and control groups in this investigation as of 1 January 1993 and the number of successful interviews.

*Follow-up for these subjects in relatively remote districts and those districts that had only one or two exposed subjects was considered difficult and financially impossible.

Discussion

This study provides information on the older members of the Yucheng cohort, who were accidentally exposed to PCB- and PCDF-contaminated rice oil, and is the first investigation of self-reported, long-term morbidity among them. There is clearly excess morbidity among the exposed subjects. Although the Yucheng victims may be motivated to over- or underre-

port illnesses, it is nonetheless useful to know what they perceive to be their experience.

Chloracne is known to be an extremely chronic condition when it results from internal rather than dermal exposure. Cases of Yusho ("oil disease" in Japanese), a similar poisoning due to ingestion of contaminated rice oil in Japan 11 years before the Yucheng episode, had acneform rash and

pigment abnormalities that lasted for many years (7,8). Other early finding of Yucheng, namely, abnormal nails, hyperkeratosis, gum swelling, gum pigmentation, and broken teeth are all much higher in exposed subjects. Skin allergy occurred approximately twice as often in the exposed group as in the control group. This was not originally noted as part of the syndrome and has not been reported in the Yusho cohort or other groups with increased exposure to similar chemicals. TCDD (dioxin), a very well-studied toxic chemical thought to act at least partially through the same receptor as PCBs and PCDFs, has been reported to activate macrophages and induce neutrophilia and an inflammatory response in murine skin (9) and augment inflammatory responses via enhanced production of tumor-necrosis factor in serum (10). However, suppressed delayed-type hypersensitivity response was also reported in guinea pigs and rats (11). In the early post-exposure years, Yucheng patients had reduced positive reaction to tuberculin skin testing (12).

Both exposed men and women reported higher rates of goiter, although neither group reported the diagnoses of hyperthyroidism or hypothyroidism more frequently. In Japanese Yusho patients 16 years after a similar exposure to PCBs and PCDFs, thyroid hormones including triiodothyronine (T_3) and thyroxine (T_4) were elevated, but

Table 1. Age, education, smoking history, and occupation of Yucheng and control subjects in Taiwan, 1993.

	Men			Women		
	Yucheng (n = 331)	Control (n = 307)	p-Value	Yucheng (n = 464)	Control (n = 386)	p-Value
Age (year distribution)	50.7 ± 12.4 ^a	51.5 ± 12.1	NS	46.9 ± 12.2	47.7 ± 12.4	NS
30–39 (%)	25	21		41	38	
40–49 (%)	28	28		23	23	
50–59 (%)	23	26	NS	19	21	NS
60–69 (%)	18	17		12	12	
> 70 (%)	6	8		5	6	
Education (years)	7.2 ± 3.9	7.0 ± 3.9	NS	5.7 ± 4.4	5.6 ± 4.3	NS
Ever smoked	193 (58.5) ^b	193 (62.9)	NS	7 (1.5)	6 (1.6)	NS
Work			NS			NS
Not working	75 (22.7)	78 (25.4)		213 (45.9)	168 (43.5)	
Agricultural	39 (11.8)	43 (14.0)		23 (5.0)	27 (7.0)	
Manufacturing	160 (48.3)	133 (43.3)		153 (33.0)	126 (32.6)	
Services	4 (1.2)	2 (0.7)		2 (0.4)	3 (0.8)	
Commercial	30 (9.1)	28 (9.1)		40 (8.6)	45 (11.7)	
Self-employed	3 (0.9)	0 (0)		3 (0.6)	3 (0.8)	
Professional	6 (1.8)	5 (1.6)		5 (1.1)	3 (0.8)	
Governmental	7 (2.1)	13 (4.2)		15 (3.2)	4 (1.0)	
Other	7 (2.1)	5 (1.6)		10 (2.2)	7 (1.8)	

NS, not significant. Average age and years of education were compared by unpaired *t*-test; age distribution, smoking history, and work were compared by chi-square test.

^aMean ± standard deviation. ^bValues shown in parentheses are percent.

Table 2. Prevalence (%) of reported diseases ever diagnosed by a physician in Yucheng and control groups in Taiwan, 1993.

	Men				Women			
	Yucheng (n = 331)	Control (n = 307)	OR	CI of OR	Yucheng (n = 464)	Control (n = 386)	OR	CI of OR
Chloracne	51 (15.4)	4 (1.3)	13.8	(5.6–46.0)	88 (19.0)	5 (1.3)	17.8	(7.9–51.0)
Hyperkeratosis	14 (4.2)	1 (0.3)	13.5	(2.7–246)	23 (5.0)	4 (1.0)	5.0	(1.9–17.1)
Abnormal nails	33 (10.0)	5 (1.6)	6.7	(2.8–19.7)	66 (14.2)	6 (1.6)	10.5	(4.9–27.4)
Skin allergy	63 (19.0)	31 (10.1)	2.1	(1.3–3.4)	106 (22.8)	39 (10.1)	2.6	(1.8–4.0)
Gum pigmentation	6 (1.8)	1 (0.3)	5.6	(0.9–107)	29 (6.3)	3 (0.8)	8.5	(3.0–35.7)
Broken tooth	29 (8.8)	15 (4.9)	1.9	(1.0–3.6)	36 (7.8)	13 (3.4)	2.4	(1.3–4.8)
Goiter	5 (1.5)	0 (0)	–	^a	17 (3.7)	7 (1.8)	2.1	(0.9–5.4) ^a
Treated with medication or surgery	4 (1.2)	0 (0)	–	^b	14 (3.0)	4 (1.0)	3.0	(1.1–10.5) ^b
Hyper- or hypothyroidism	1 (0.3)	1 (0.3)	0.93	(0.04–23.5)	10 (2.2)	5 (1.3)	1.7	(0.6–5.4)
Headache	18 (5.4)	4 (1.3)	4.4	(1.6–15.2)	42 (9.1)	17 (4.4)	2.2	(1.2–4.0)
Treated with medication	14 (4.2)	2 (0.7)	6.7	(1.9–43.0)	14 (3.0)	10 (2.6)	1.2	(0.5–2.7)
Anemia	3 (0.9)	4 (1.3)	0.7	(0.1–3.2)	45 (10.0)	17 (4.4)	2.3	(1.3–4.3)
Treated with medication	1 (0.3)	3 (1.0)	0.3	(0.02–2.4)	24 (5.2)	9 (2.3)	2.3	(1.1–5.2)
Arthritis	25 (7.6)	6 (2.0)	4.1	(1.8–11.2)	37 (8.0)	24 (6.2)	1.3	(0.8–2.3)
Treated with medication or surgery	16 (4.8)	5 (1.6)	3.1	(1.2–9.5)	23 (5.0)	15 (3.9)	1.3	(0.7–2.6)
Herniated disc	18 (5.4)	6 (2.0)	2.9	(1.2–8.0)	15 (3.2)	8 (2.1)	1.6	(0.7–4.0)
Treated with medication or surgery	13 (3.9)	3 (1.0)	4.1	(1.3–18.2)	5 (1.1)	5 (1.3)	0.8	(0.2–3.0)
Hypertension	28 (8.5)	23 (7.5)	1.1	(0.6–2.0)	45 (9.7)	29 (7.5)	1.3	(0.8–2.2)
Treated with medication	14 (4.2)	10 (3.3)	1.3	(0.6–3.1)	28 (6.0)	18 (4.7)	1.3	(0.7–2.5)
Diabetes mellitus	14 (4.2)	11 (3.6)	1.2	(0.5–2.7)	15 (3.2)	10 (2.6)	1.3	(0.6–2.9)
Treated with medication	13 (3.9)	9 (2.9)	1.4	(0.6–3.3)	10 (2.2)	8 (2.1)	1.0	(0.4–2.8)
Coronary disease	4 (1.2)	3 (1.0)	1.2	(0.3–6.3)	4 (0.9)	1 (0.3)	3.3	(0.5–65.6)
Treated with medication	3 (0.9)	2 (0.7)	1.4	(0.2–10.6)	4 (0.9)	1 (0.3)	3.3	(0.5–65.6)
Liver disease	28 (8.5)	20 (6.5)	1.3	(0.7–2.4)	23 (5.0)	17 (2.9)	1.8	(0.9–3.8)
Treated with medication	19 (5.7)	13 (4.2)	1.4	(0.7–2.9)	13 (2.8)	6 (1.6)	1.8	(0.7–5.2)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aOR = 2.8 and CI, 1.2–7.1 if men and women were combined. ^bOR = 4.0 and CI, 1.5–13.9 if men and women were combined.

Table 3. Lifetime prevalence of medical conditions (%) and 1980–1982 polychlorinated biphenyl (PCB) levels in Yucheng individuals without (-) or with (+) reported chloracne.

	Women			Men		
	Chloracne		p-Value	Chloracne		p-Value
	-(n = 376)	+(n = 88)		-(n = 280)	+(n = 51)	
Gum pigmentation	2.7	21.6	< 0.0001	0.3	9.1	< 0.0001
Abnormal nails	6.7	46.6	< 0.0001	6.8	27.5	0.0001
Skin allergy	18.9	39.8	0.0001	15.4	39.2	0.0002
Hyperkeratosis	2.4	15.9	< 0.0001	1.8	18.7	< 0.0001
Anemia	7.5	19.3	0.0018	1.1	0	NS
Headache*	8.8	10.2	NS	5.0	7.8	NS
Arthritis	8.0	8.0	NS	6.8	11.8	NS
Herniated disc**	2.4	6.8	0.028	5.4	5.9	NS
Hyper- or hypothyroidism	2.1	2.3	NS	0.4	0	NS
Thyroid goiter [†]	3.2	5.7	NS	1.1	3.9	NS
PCB levels (ppb)	69.0	106.6	0.012	67.7	103.9	0.012
in 1980–1982 [‡]	(7.0) ^b	(13.1)		(6.1)	(12.9)	

NS, not significant.

^aBased on 350 Yucheng women and 255 Yucheng men in whom serum levels of PCBs were available. ^bValues in parentheses are standard error. **p* = 0.016; ***p* = 0.019; [†]*p* = 0.025 with men and women grouped together.

not to a level suggesting clinical hyperthyroidism (13). This is compatible with our finding that prevalence of reported hypothyroidism or hyperthyroidism in the exposed group was not different from that in the control group. Goiter was not reported as a significant finding in Yusho patients. In rodents, dioxins and PCBs induce activity of uridine diphosphate glucuronyltransferase, which metabolizes T₄ (14). Secretion of thyroid-stimulating hormone (TSH) may be increased secondary to decreases of circulating T₄ levels. Prolonged elevation of TSH may lead to hyperplasia and hypertrophy of the thyroid. The extreme of this effect might be TSH-related thyroid tumors, which has been reported in both rats and mice after exposure to TCDD (15,16).

The increased reports of joint and spine diseases is especially prominent in exposed men. This does not seem to be due to overreporting because these conditions were not reported more frequently in exposed women. The possibility of degenerative or traumatic arthritis secondary to occupational acute and chronic injuries is not very likely because the Yucheng and control groups had similar occupational backgrounds (Table 1). Although autoimmune-mediated arthritis cannot be ruled out, immunologic evaluation in the early years after exposure actually showed suppressed serum IgA and IgM and decreased helper-T cells, which had returned to normal levels 3 years later (12). TCDD has been reported to cause atrophy of the thymus and suppression of thymus-dependent immunity, both of which are mediated by binding to the aryl hydrocarbon (Ah) receptor present in the epithelial cells of the thymus (17). Evidence for potential autoimmunity caused by dioxin-like chemicals includes the report that injection of TCDD to the footpads of rats induced mild follicular hyperplasia in the popliteal lymph nodes

(18). In humans, clear evidence for TCDD or PCB-induced immunologic diseases has not been reported. Immune-mediated inflammatory reaction and arthritis can be caused by chemical exposure. Both PCB congeners and dioxin-like dibenzofuran congeners interact with hormones and hormonal receptors (19,20). Whether these endocrine-disrupting effects induce osteoporotic changes in exposed men, which in turn causes increased spine and joint diseases, warrants further investigation. The finding of easily fractured teeth may or may not be related to osteoporosis. Similar findings have been described in prenatally exposed Yucheng children (21). However, all of the directly exposed subjects were old enough to have calcified permanent teeth at the time of exposure, so the mechanism is unclear.

Headache was also more commonly reported by both exposed men and women. This finding was compatible with previous reports that headache and other neurologic symptoms were among the early symptoms of Yucheng intoxication (22). There were 2.3 times more exposed women who reported anemia and required medication for anemia. Because some PCBs are weak estrogens, the anemia limited to women may implicate some relation to menstrual blood loss. Because data on the young women are needed to further evaluate this finding, we have begun locating and interviewing them.

When chloracne was compared with other medical findings, there was some statistically significant clustering of symptoms, especially skin complaints (Table 3). However, except for hyperkeratosis and gum pigmentation, very specific markers of exposure, excess symptoms were not observed only in those with chloracne, indicating that different subgroups in the Yucheng cohort were probably susceptible to different medical ailments. Further study,

including medical examination and genetic evaluation, is needed to clarify the relationship between individual susceptibility and health outcomes in the exposed population.

Some negative findings are reassuring. There is not yet excess cancer mortality or incidence in this cohort, as there was in Yusho as early as 9 years after exposure. A 15-year follow-up of 1,761 Yusho subjects revealed increases in liver cancer mortality in both sexes and lung cancer mortality in men (23). This difference may be because the Taiwan Yucheng cohort was so young at exposure. There do not appear to be higher rates of infection, which was seen in the transplacentally exposed children (24), despite the well-known immunosuppressive potential of these chemicals and the documented early immunologic changes (12). There also does not appear to be continuing symptomatic conjunctivitis, which was quite severe soon after the outbreak, or peripheral neuropathy, which was also seen earlier (22).

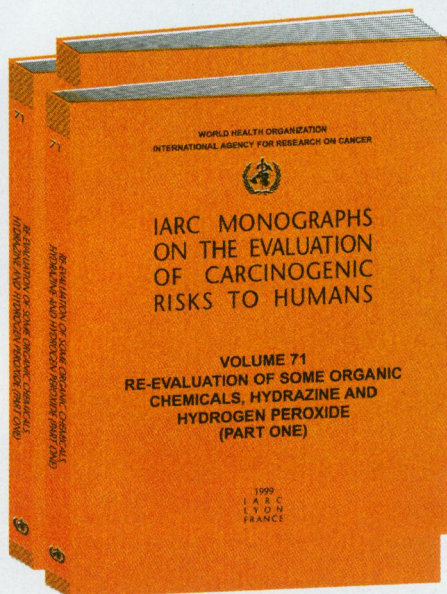
Common diseases such as hypertension, diabetes mellitus, coronary heart disease, and lung diseases appeared to be similarly frequent in the exposed and control groups. This is different from findings from a population heavily exposed to TCDD by inhalation in Seveso, Italy; in this population, mortality secondary to cardiovascular diseases, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) in men and secondary to hypertensive disease, COPD, and diabetes in women was increased (25). A group of U.S. Air Force veterans exposed to Agent Orange and its contaminant TCDD during the Vietnam War, "Operation Ranch Hand" veterans, were also found to have increased diabetes, glucose intolerance, and serum insulin abnormalities (26). Due to the young age of the Yucheng cohort, occurrence of coronary diseases, hypertension, and diabetes mellitus was low; thus, there was little statistical power to detect differences.

This episode, while a public health disaster, has also been an important setting to examine the long-term consequences of exposure to high doses of these very widely dispersed chemicals to a community at large. Most other information comes from mortality studies of PCB workers, but they receive exposures as adults, are usually mostly male, and are exposed to uncontaminated PCBs. This study provides a preliminary picture of the Yucheng cohort who had high exposures to PCBs/PCDFs in 1979 and continuing internal exposure because these compounds are so poorly excreted. Excessive medical problems including skin diseases, goiter, anemia, and joint and spine diseases were reported by this cohort. Further clinical evaluation of those conditions found in excess is warranted.

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