

2. Studies of Cancer in Humans

Human beings have not been documented to have been exposed to toxicologically significant amounts of PCDFs alone. There have been two food poisonings in Asia in which PCBs contaminated by PCDFs were the etiological agent. The blood levels of PCBs of the victims in these incidents were higher than those of the general population but lower than are seen in highly exposed workers. [The Working Group noted that several cohorts with occupational exposure to PCBs have been followed; there is some evidence of increased incidence of liver and biliary cancer combined but not increased primary liver cancer (Brown, 1987).] The morbidity experienced by the poisoning victims was greater than is usually seen in PCB workers, and this difference in toxicity is usually attributed to the admixed PCDFs. Strictly, though, inferences about the toxicity of PCDFs, PCBs, or any component of the oil are not justified, since all the victims were exposed to all components. There has also been exposure to PCDFs in accidents, such as the Binghamton, NY, fire (see Section 1.2.1(b)(viii)), but they have been in situations in which there was also documented exposure to 2,3,7,8-TCDD, other PCDDs, PCBs, and other compounds.

The most toxic PCDFs are estimated to have a potency within one or two orders of magnitude of that of 2,3,7,8-TCDD. Thus, for some groups with environmental exposures, such as consumers of Baltic Sea fish, PCDFs may make up the major part of their potentially toxic exposures as estimated by total TEQs.

2.1 Rice oil contamination incidents

The poisoning incidents in Japan and Taiwan involving consumption of contaminated rice oil are described in Section 1.3.1(b)(i).

2.1.1 Japan

In 1968, in Fukuoka and Nagasaki, Japan, there was an outbreak of an illness consisting of severe cystic acne, hyperpigmentation and conjunctivitis. Clinical and epidemiological investigation showed a strong association with the consumption of specific lots of rice bran cooking oil (Kuratsune *et al.*, 1972). The illness was termed 'yusho', Japanese for 'oil disease'. Initially, chemical analysis could show only that there was a large amount of chlorine in the oil; the contaminant was later shown to be PCBs and related compounds.

Eventually about 2000 cases were registered with Japanese health authorities. The reasons for registration included not only epidemiological surveillance but also clinical care and in some cases eligibility for compensation. [The Working Group noted that some people who were genuine cases may have avoided registration, and some with

minimal exposure may be included, but the combination of general publicity and the linking of registration to care probably means that most of those eligible were registered.]

The Japanese oil contained of the order of 1000 mg/kg PCBs and 5 mg/kg PCDFs. Estimates of intake are based on a study of 141 cases (Masuda, 1994). These patients consumed about 500 mL oil before becoming symptomatic, and about another 200 mL before the cause of the illness was determined and oil consumption ceased. Thus, they ingested about 500 mg PCBs and 2.5 mg PCDFs before becoming symptomatic, and about 600 mg PCBs and 3.5 mg PCDFs in total. This occurred over a period of weeks.

Ikeda and Yoshimura (1996) followed 1815 *yusho* patients identified from the registry from the Japanese Ministry of Health and Welfare to the end of March 1990. They then contacted the local health departments and obtained a copy of the death certificate for each of those who had died. The causes of death, standardized mortality ratios (SMRs) and confidence intervals (CIs) are presented in **Table 25**. The overall analysis used Japanese national data for its comparison group, but regional data were used for specific cancer sites in order to see whether regional variations explained observed excesses in mortality. The SMR for total mortality was 1.1 [95% CI, 0.9–1.2]; for total cancer in men, it was 1.6 [95% CI, 1.2–2.1]; and, for liver cancer in men, it was 3.4 [95% CI, 1.8–6.0]. Women had decreased total cancer mortality but a nonsignificant increase in liver cancer mortality (SMR, 2.3; [95% CI, 0.5–6.7]) based on three deaths. There was no excess mortality from cancer in women. Both sexes showed a nonsignificant excess mortality from non-malignant liver disease.

2.1.2 Taiwan

Although the rice oil processing machines were banned in Japan, at least one found its way to Taiwan. In 1979, an extraordinary replication of the Japanese incident occurred there (Hsu *et al.*, 1985), called '*yucheng*', meaning 'oil disease' in Chinese, again involving about 2000 persons.

The Taiwanese oil contained about 100 mg/kg PCBs and 0.4 mg/kg PCDFs. Estimates are based on a study of 99 cases. Patients consumed about 300 mg PCBs and 1.3 mg PCDFs during latency and about 1 g PCBs and 3.8 mg PCDFs in total (Hsu *et al.*, 1994). Some persons consumed the oil for six months before becoming symptomatic. The ratio of PCBs to PCDFs was similar in the *yusho* and *yucheng* episodes, and the dose of PCBs and PCDFs causing symptoms was roughly similar, although the Taiwanese consumed more oil that was less contaminated.

Yu *et al.* (1996) reported that a total of 2061 subjects were included in the *yucheng* registry by 1983; no cases were added nor active follow-up carried out after that year. They acquired the registry and traced cohort members through 31 December 1991. For the deceased cases, they acquired a copy of the death certificate from the local household registration offices and abstracted information on date, place and cause of death. The overall and cause-specific mortality of the exposed group was compared with that of the Taiwan general population using 1 January 1979 as the date of the incident and, as the end of follow-up, 31 December 1991, the date of death or the last date a subject was

known to be living. Of the 2061 subjects in the 1983 *yucheng* registry, 70 were actually offspring of the exposed subjects who were born after 30 June 1978 and were excluded. Of the remaining 1991 *yucheng* subjects, 154 did not have valid addresses and thus could not be traced; therefore, a total of 1837 *yucheng* subjects were included. Vital status was determined for 99.5%; 83 of the subjects had died during the follow-up period. The SMR for total mortality was 0.8 (95% CI, 0.7–1.0). There were 10 cancer deaths (SMR, 1.2; 95% CI, 0.6–2.3) including three from liver cancer (SMR, 0.8; 95% CI, 0.2–2.4). There was a 2.7-fold (1.3–4.9) excess of cirrhosis and non-malignant liver disease, based on 10 deaths. Hsieh *et al.* (1996) independently studied the Taiwanese cohort during the same time period and came to similar conclusions.

Table 25. Follow-up studies of mortality in the Asian PCB/PCDF poisonings

	<i>Yusho</i> (Japan)		<i>Yucheng</i> (Taiwan)			
	Ikeda & Yoshimura (1996)		Yu <i>et al.</i> (1996)		Hsieh <i>et al.</i> (1996)	
Number	1815		1837		1940	
Male	816		851		929	
Female	899		986		1011	
Years of follow-up	1968–90		1979–91		1979–91	
Median age at exposure	[~ 25 years]		[~ 22 years] (46% were < 20 years old)		[~ 22 years]	
Deaths	No.	SMR (95% CI)	No.	SMR (95% CI)	No.	SMR (95% CI)
Total deaths	200	1.1 [0.9–1.2]	83	0.8 (0.7–1.0)	102	1.1 (0.9–1.3)
Male	127	1.2 [1.0–1.4]	47	0.8 (0.6–1.1)	55	1.0 (0.8–1.3)
Female	73	0.9 [0.7–1.1]	36	0.9 (0.6–1.2)	47	1.3 (1.0–1.8)
Cancer deaths	58	1.2 [0.9–1.6]	10	1.2 (0.6–2.3)	11	0.6 (0.3–1.0)
Male	45	1.6 [1.2–2.1]	8	1.6 (0.7–3.2)	8	0.7 (0.3–1.4)
Female	13	0.7 [0.3–1.0]	2	0.6 (0.1–2.3)	3	0.4 (0.1–1.2)
Liver cancer deaths	15	3.1 [1.7–5.1]	3	0.8 (0.2–2.4)	2	0.7 (0.1–2.5)
Male	12	3.4 [1.8–6.0]	2	0.7 (0.1–2.5)	1	0.3 (0.0–1.6)
Female	3	2.3 [0.5–6.7]	1	1.3 (0.02–7.1)	1	1.1 (0.0–6.0)
Liver disease deaths	9	1.8 [0.8–3.5]	10	2.7 (1.3–4.9)	15	3.2 [1.8–5.3]
Male	6	1.7 [0.6–3.6]	7	2.5 (1.0–5.1)	9	2.5 [1.2–4.8]
Female	3	2.3 [0.5–6.7]	3	3.4 (0.7–9.8)	6	5.2 [1.9–11.4]

[] Calculated by the Working Group

2.1.3 Comparison of Japan and Taiwan

The cancer findings in the 12-year follow-up data from Taiwan are not consistent with the 22-year follow-up data from Japan. There was a clear excess of liver cancer mortality in males in Japan that was not seen in Taiwan. The excess of liver cancer was even greater in the Japanese data at 15 years of follow-up (Ikeda *et al.*, 1986) (SMR, 5.6) than it was at 22 years (SMR, 3.4). Both cohorts showed an excess of non-malignant

liver disease. The exposures to the heat-degraded PCBs appear to have been similar. Masuda (1994) showed that the differences in blood levels of PCBs and PCDFs reported between *yusho* and *yucheng* were a function of the time after the incident that the samples were drawn, rather than due to differences in exposure. The methods of cohort selection and follow-up do not appear to favour ascertainment of those with cancer in Japan compared with those in Taiwan. The belief among physicians that the status of being a *yusho* (or *yucheng*) case increases cancer risk, leading to a more frequent diagnosis, cannot be ruled out. However, such a diagnostic bias would have to be specific to Japan and to liver cancer to produce the observed effect. Liver disease and liver cancer are common in both countries, and the recognition and management of them is a regular part of clinical training. It is unlikely that liver cancer is being under-diagnosed among the Taiwanese.

Chronic hepatitis B infection confers a relative risk of as high as 100 for liver cancer. In the 1970s and 1980s, Japan as a whole probably had about a 2% seroprevalence for antibody to hepatitis B surface antigen, while Taiwan had about 15% (IARC, 1994a). It is therefore unlikely to be a confounder.

Hepatitis C virus is probably more prevalent in Japan than in Taiwan (IARC, 1994b). Ito *et al.* (1991), in a community-based survey of Japanese over the age of 40 years, showed a prevalence of 2.3% using a (relatively non-specific) first-generation ELISA assay. In Taiwan, Lin *et al.* (1991) showed a prevalence of 0.6% in pregnant women using a second-generation recombinant immunoblot assay. Thus, Japan has a four-fold higher rate, but the prevalences are low. Hepatitis C appears to be as carcinogenic as hepatitis B but, unless there is a different chemical interaction with the two viruses (for which there is no evidence), the difference in prevalence cannot account for the liver cancer excess in *yusho* patients in Japan.

Hepatitis B and possibly C infection increases dramatically at lower latitudes, and the prefectures of Japan involved, Nagasaki and Fukuoka, are southern ones. Relatively minor differences in the prevalence of hepatitis virus infection could readily produce a relative risk of 3 for liver cancer, since the national rates are dominated by the population centres further north. Ikeda and Yoshimura (1996), however, considered this possibility and found that, when the liver cancer rates among *yusho* patients were compared with the Nagasaki and Fukuoka rates, the relative risk declined from 3.4 to 2.3 in men but remained statistically significant. This may be too conservative, since only about half of the cases actually lived in Nagasaki and Fukuoka.

2.2 Fish consumption

Swedish investigators have studied mortality and cancer incidence in Swedish fishermen and their wives (Rylander & Hagmar, 1995) from the Baltic coast, who prefer salmon, herring and other fatty fish, and compared them both with the rates in the Swedish population (Hagmar *et al.*, 1992) and those of fishing families from the Atlantic coast, who prefer less fatty cod and flat fish (Svensson *et al.*, 1995a). Swedish fishermen were believed to eat about twice as much fish as the general population, and this was confirmed by dietary interviews in a sample of the wives. Baltic fish are contaminated by

organochlorine compounds, and the concentration of these substances in human body fat relates to the amount of fish consumed. The predominant exposure in terms of PCDDs and PCDFs from fatty fish from the Baltic Sea is to 2,3,4,7,8-PeCDF (Svensson *et al.*, 1991) [although even heavy fish consumers probably have body fat concentrations about three orders of magnitude lower than those of the victims of the Asian poisonings]. These fish also contain PCBs and other persistent chlorinated compounds.

The fishermen (> 99% of the cohort members were men) cohorts were formed from the records of the local fishermen's organizations. For the Atlantic coast, 8493 persons (16 women) had ever been members of the organization and, for the Baltic coast, 2907 persons (24 women). The cohorts consisted of 8477 Atlantic coast and 2896 Baltic coast fishermen observed from 1965 for the Atlantic and from 1968 for the Baltic. After the fishermen were identified, the wives were sought through linkage to the national Swedish population registry and also records in local parishes. For the Atlantic coast, 7166 women were identified who either were or had been married to one of the fishermen. For the Baltic coast, there were 2175 women. Information was updated for everyone to 31 December 1988, including a subset of the Baltic coast men who had been reported on previously (Hagmar *et al.*, 1992). Data on death came from Statistics Sweden and those on cancer occurrence from the Swedish Cancer Registry (Svensson *et al.*, 1995b).

Stomach cancer occurred more frequently in the Baltic coast fishermen. Compared with the regional population, the standardized incidence ratio (SIR) was 1.6 (95% CI, 1.0–2.4) and, compared with Atlantic coast fishermen, the incidence rate ratio (IRR) was 2.2 (1.3–3.5). Squamous-cell cancer of the skin was diagnosed more frequently in the Baltic coast fishermen (SIR, 2.3; 1.5–3.5) compared with the regional population and (IRR, 1.9; 1.2–3.1) compared with the Atlantic coast fishermen. Both cohorts of fishermen had higher mortality from multiple myeloma compared with the general population, with SMRs of 3.1 on the Baltic coast and 1.3 on the Atlantic coast. Ischaemic heart disease was decreased among the Baltic coast fishermen but not among those from the Atlantic coast, consistent with their reported differences in diet and the possible protective role of *n*-3 polyunsaturated fatty acids found in the fatty fish preferred by the former population (Svensson *et al.*, 1995b). Compared to the Swedish rates, the Baltic coast wives had a slightly higher and the Atlantic coast wives a slightly lower incidence of breast cancer, but comparisons with neither the population nor the other group were significant (Rylander & Hagmar, 1995).

2.3 Industrial cohorts

[The Working Group noted that exposure to PCDFs may have occurred among workers in the phenoxy herbicides/chlorophenols industrial production cohorts which have been reviewed in the monograph on PCDDs. Exposure to PCDFs, however, is inadequately characterized in these cohorts. Furthermore, the Working Group considered that confounding by concomitant exposure to PCDDs seriously complicates any interpretation of these data regarding cancer risk in relation to PCDF exposure.]