Gaffey, W.R. "Recent Epidemiologic Studies of PCBs", Advances in Exposure, Health & Environmental Effects Studies. PCBs (1983):189-201 NTIS PB84-135771

RECENT EPIDEMIOLOGIC STUDIES OF PCBS

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Before the Yusho incident in 1968, published studies of the health effects of PCBs, with the exception of Meigs et al (1954), were essentially clinical studies of occasional accidental severe exposures. In the following decade ten epidemiologic studies were published (in addition to the many reports on the Yusho incident itself), all but one of which dealt with occupationally exposed populations, and only one of which studied the relationship between cancer and PCB exposure (Gaffey, 1982).

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2 PCB EPIDEMIOLOGY

Since 1978 there have been ten epidemiologic studies of the health effects of PCBs. Seven of these are cross-sectional investigations of symptoms and biochemical parameters. Of these, five are occupational, one is a study of both occupational and non-occupational exposure, and one is non-occupational. The remaining three reports are cohort mortality studies of occupationally exposed groups. In addition, there has been a report on cancer mortality in the Yusho population.

This paper briefly summarizes the status of the epidemiologic evidence on health effects as of 1978, and reviews and evaluates the subsequent studies in detail.

THE EVIDENCE AS OF 1978

The Yusho incident of 1968 at first appeared to be a classic example of the effects of a massive ingestion of PCBs. Over 1000 Japanese became ill after eating a cooking oil contaminated with Kanechlor 400, a PCB compound of Japanese manufacture. The most common acute symptoms observed were hyperpigmentation and acne-like lesions, central nervous system symptoms, discharge from the eyes, and vomiting and diarrhea. These symptoms were dose related, and some of them persisted for as long as six years. Laboratory tests showed disturbances of liver function and fat metabolism, and there were clinical reports suggestive of some abnormalities in the children of Yusho mothers (NIOSH, 1977).

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As of the end of 1977, 51 deaths among Yusho patients had been identified, with an apparent excess of cancer deaths (Urabe et al, 1979). However, the data were not adjusted for age, and the completeness of ascertainment of the deaths is not known. The elapsed time from the original incident to the reported deaths (one decade) was short enough to cast doubt on whether the cancers could in fact have arisen from the Yusho exposure.

In any case, in the decade following the Yusho incident analytic techniques for identifying PCBs and allied compounds improved considerably, and the cooking oil was reanalyzed. The new analyses showed that the Yusho patients had in fact ingested about the same amount of polychlorinated dibenzofurans (PCDFs) as of PCBs, in addition to polychlorinated quater-phenyls (PCQs). Current determinations of blood and tissue levels of these other compounds in Yusho patients have shown total levels about equal to that of PCBs (Kimbrough, 1980). It therefore appears that the epidemiologic findings in the Yusho incident should properly be attributed to the more toxic PCDF rather than to PCBs.

There were nine other published cross-sectional studies of symptoms and biochemical parameters related to PCB exposure, one of which was non-occupational, and one occupational study of cancer morbidity and mortality.

In summary, the occupational studies found chloracne or other dermatitis, and mild liver function abnormalities

in the absence of clinical illness, to be associated with PCB exposure. Two studies of cholesterol levels gave contradictory results, and one study of triglyceride levels showed an increase. The non-occupational study showed no association between blood PCB levels and any of the Yusho symptoms, but did not examine liver function or fat metabolism.

The cancer study found an apparent excess of malignant melanoma based on three cases, but was later withdrawn because of concern about whether the exposed population had been correctly identified.

RECENT STUDIES

The seven cross-sectional studies completed since 1978 address a broader range of health effects than did the pre-1978 studies, and in some cases used formal statistical techniques to take account of confounding variables such as age, sex and weight. Two of the studies, Fischbein et al (1979) and Smith et al (1982) evaluated their findings in relation to higher chlorinated and lower chlorinated PCBs separately. The studies' findings can be classified under five general headings; dermatologic effects, liver function, fat metabolism, other objective findings, and reported symptoms and illnesses. The cohort mortality studies, although they collected data on all causes of death, were concerned primarily with cancer.

Dermatologic Effects

Table 1 summarizes the results of the five studies that reported on dermatologic effects. The negative study of Baker et al (1980) examined 18 exposed workers, 19 members of their families, and 89 community residents with exposure to fertilizer containing PCBs. The rest were occupational studies, two of which found chloracne and all of which found dermatitis.

Fischbein et al (1979) reported that 50 percent of 326 capacitor manufacturing workers reported a history of dermatological symptoms, the most common being a rash. Those with symptoms had higher blood levels of high chlorinated PCBs. Maroni et al (1981 II) reported ten cases of dermatitis (five diagnosed as active or past chloracne) in 80 exposed workers, but provided no further data on the blood PCB levels of those with dermatitis vs. those without. Chase et al (1982) found increased dermatitis, and some chloracne, in the most exposed group out of 120 railroad maintenance workers, but within the group found no significant association with blood or fat PCB levels. Smith et al (1982), in a study of 92 employees of two utility companies, found no consistent association between dermatitis and either high or low chlorinated blood PCB levels.

Although the data are not consistent, they suggest that there may be a gross dose response relationship between dermatitis and blood levels of PCBs, possibly

complicated by variations in individual susceptibility and in work habits that may affect absorption of PCBs through the skin.

Liver Function

Table 2 shows the results of the six studies that investigated liver function. The two non-occupational studies showed no liver function anomalies associated with blood PCB levels. The first one did not adjust for confounding variables (Baker et al, 1980). The second, a study of 458 residents of a community with high environmental levels of PCBs, found an association which disappeared when age and alcohol consumption were taken into account (Kreiss et al, 1981).

Of the four occupational studies, three showed various liver function anomalies related to blood PCB levels. Chase et al (1982) adjusted the results for age. Smith et al (1982) adjusted the data for age and sex. The latter study showed a significant association of liver function anomalies with low chlorinated blood PCBs in one of the two plants studied but not in the other. Maroni et al (1981 II) found liver abnormalities associated with elevated blood PCB levels, but the liver abnormalities were defined as liver function anomalies or liver related symptoms or clinical findings of abnormality. They state that "only in a few cases was a well-defined liver failure (presence of symptoms, hepatomegaly, and abnormal liver findings) present."

Fischbein et al (1979) found no liver function anomalies associated with exposure, and in fact commented on the "paucity of abnormal results" in their biochemical studies.

With the exception of Maroni et al, the occupational studies agree in finding few or no liver function abnormalities, and no associated clinical illness.

Fat Metabolism

Table 3 summarizes the results of the five studies that examined fat metabolism. Fischbein et al (1979) found no association between cholesterol or triglycerides and blood PCBs. Kreiss et al (1981) found an increase in cholesterol with increasing blood PCB levels, but no relationship of triglycerides to blood PCBs when an adjustment was made for cholesterol level. Two other studies, Baker et al (1980) and Chase et al (1982) agree that cholesterol is not associated with blood PCBs but that triglycerides are.

Smith et al (1982) found cholesterol levels to be positively associated with low chlorinated PCBs in one of the two plants studied. Triglycerides were positively associated with high chlorinated PCBs in one plant and negatively associated in the other, where they were positively associated with low chlorinated PCBs.

The preponderance of evidence is that cholesterol is not associated with blood PCBs. There is no obvious

explanation for the association of cholesterol and blood PCBs found by Kreiss et al. However, their use of cholesterol as an adjustment factor for triglycerides implies that they view cholesterol as an independent variable that predicts triglycerides. The results of Baker et al and Chase et al do not support this view, since they show that the putative predictor, cholesterol, is not associated with blood PCB levels while triglyceride levels are. The association between triglycerides and blood PCB levels appears to be ambivalent at the least.

Other Objective Findings

Fischbein et al (1979), Baker et al (1980) and Maroni et al (1981 II) examined blood chemistry and found no association with blood PCB levels.

Kreiss et al (1981) found a statistically significant positive association between diastolic blood pressure and blood PCBs after adjusting for cholesterol, triglycerides, smoking and race. However, Smith et al (1982) reported no such association.

Warshaw et al (1979) reported decreased vital capacity in 243 capacitor manufacturing workers compared with published reference standards. However, most of the study population were current or former smokers, while the reference standard is based on a non-smoking population. The effects of smoking could be sufficient to explain the findings.

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Reported Symptoms and Illnesses

Six of the studies investigated a range of symptoms and illnesses. Two of them reported positive findings in occupationally exposed populations. Fischbein et al (1979) reported a history of gastrointestinal symptoms in 18 percent of 326 capacitor manufacturing workers, a prevalence of from 3.0 to 15.2 percent of various musculo-skeletal symptoms, and a prevalence of from 4.8 to 27.8 of various neurological symptoms. These were, however, unrelated to blood PCB level or duration of employment. Maroni et al (1981 II) reported eight cases of gastro-intestinal complaints in 80 exposed workers with no indication of whether there was a relationship to blood PCB level or duration of employment. They also reported two bleeding haemangiomas and one case of chronic myelocytic leukemia.

The other four studies reported no PCB related findings. Specifically Baker et al (1980) found no relationship with any of the following; fever, weight loss, anorexia, fatigue, headache, eye irritation, cough, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, arthralgia and persistent rash. Kreiss et al (1981) reported the same thing for prevalence of illness or weight loss in the previous year, use of medication, use of medical care, history of heart disease, and percentage of pregnancies ending in miscarriage, stillbirth or infant death.

Chase et al (1982) failed to find any evidence of organ toxicity in a review of the medical histories and physical findings in a group of exposed railroad maintenance workers, and Smith et al (1982) reported no consistent dose-dependent increase in either symptoms or past illnesses. Their inquiry covered digestive, respiratory, central and peripheral nervous system, dermatologic, and emotional symptoms.

The evidence shows no PCB related symptoms or illnesses, since the two reports out of six that mentioned symptoms failed to show an association with level or duration of exposure.

Carcinogenicity

Table 4 shows the major findings of cancer mortality in three cohort studies of PCB exposed workers. Brown et al (1981) studied a cohort of capacitor manufacturing workers in two plants who had been exposed at least three months between 1946 and 1975 inclusive in one plant or between 1940 and 1975 inclusive in the other. Follow-up was more than 97 percent complete as of the end of 1975, and expected mortality was calculated from U.S. population rates. Non-statistically significant excesses were found for rectal cancer, based on four deaths, and liver cancer, based on three deaths. The rectal cancers showed a slight increase with an increase in the latency period, but the liver cancers showed no consistent trend. There were no

increases in mortality from these causes associated with increasing lengths of exposure.

Bertazzi et al (1981) also studied a cohort of capacitor manufacturing workers in a plant near Milan. The cohort consisted of every person who had worked for at least six months between 1946 and 1970, inclusive, except for clerical workers. Follow-up was over 98 percent complete as of the end of 1978, and expected mortality was based on rates in the city where the plant was located. Data were analyzed separately for male (290) and female (1020) workers. A statistically significant excess mortality from all cancers, based on eight deaths, was found in male workers, and a statistically significant excess for all causes was found in female workers, based on 15 deaths. There were non-significant excesses of lymphatic and hematopoietic cancer in both sexes, based on four deaths, and of digestive cancer in males, based on three deaths. The sites involved in the digestive cancer deaths were stomach, pancreas and biliary tract. No analysis by duration or latency of exposure was attempted because of the small numbers involved. The authors note that the cohort was very young, and that their follow-up will be continued.

Zack et al studied all hourly male workers who had been employed in the manufacture of PCBs in a general chemical plant for at least six months between 1945 and 1965 inclusive. Follow-up was approximately 99 percent

complete (one person was lost) as of the end of 1977, and expected mortality was calculated from U.S. population rates. There were eight cancer deaths. The only noteworthy finding was a non-statistically significant excess in lung cancer based on four deaths. No liver cancer deaths were found.

DISCUSSION

Doll (1981) has suggested criteria for establishing carcinogenicity from epidemiologic evidence. They are similar to those proposed by the International Agency for Research on Cancer (1980) and are essentially as follows; (1) there is an excess in exposed groups beyond what can be expected by chance, (2) there is an appropriate relationship with dose or duration of exposure, (3) there are no known biasing or confounding factors, (4) the association is observed repeatedly in different circumstances. The development of these criteria was stimulated by a concern to provide generally accepted guidelines for establishing carcinogenicity, but they apply equally well to other health outcomes.

Criteria for establishing the absence of a health effect are inherently more difficult. The cliché that it is impossible to prove a negative is true but misleading, in the sense that it is also impossible to prove a positive association by means of epidemiologic studies. A statistically significant positive finding allows us to conclude

that an association exists, with a known probability that the conclusion is wrong. Repeated positive studies reduce that probability in a manner that can be calculated, but there remains a chance that the finding is false. On the other hand, a negative study allows us to conclude that there is no association, with a probability of error that depends on how great an association really might exist. Repeated negative studies reduce this probability, but there is always a large probability that a very small effect might not be detected. Therefore both positive and negative studies carry a risk of error, although in both cases the strength of the evidence may be such as to make that chance negligibly small.

Cross-sectional Studies 16 studies both pre and post 1977

There is a reasonable consensus that dermatitis is associated with occupational exposure to PCBs, although the dose response relationship has not been established in all of the studies. Two non-occupational studies agree that there is no dermatitis associated with environmental, i.e., non-occupational exposure. The difference in the results of the occupational and non-occupational studies is consistent with the order-of-magnitude differences in the exposures of the two groups.

There is a similar preponderance of evidence that mild liver function anomalies are associated with occupational but not with non-occupational exposure. One occupational

study found associated clinical symptoms, but the remaining three studies found no detectable clinical illness. By Doll's criteria of consistency, it is very unlikely that clinical illness is associated with the anomalies found in occupationally exposed populations.

Findings concerning cholesterol levels again show a preponderance of evidence that cholesterol levels are not associated with blood PCB levels, even though one non-occupational study did report an association.

The situation with respect to triglyceride levels is slightly more ambiguous. Two out of five studies, including one non-occupational study, found a relationship with blood PCBs, so that the possibility that such a relationship really exists must be considered.

Studies of blood chemistry were uniformly negative. Two studies of diastolic blood pressure gave contradictory results. One study of pulmonary function suffered from a failure to account for smoking so that its findings cannot be attributed to PCB exposure. None of these areas of study appear to show any relationship to PCB exposure.

None of the six studies of reported illnesses and symptoms constitute evidence by Doll's criteria. Four studies showed no relationship of a wide range of symptoms to PCB exposure. Two occupational studies reported various symptoms, but did not show that they were related to blood PCB level or duration of employment.

Cohort Cancer Studies

The most noteworthy characteristic of the three mortality studies is that they do not agree with each other. Excess cancer of the liver, rectum, stomach, pancreas, biliary tract and lung are each found in one of the studies but in none of the others.

Although the power of the studies is limited (the most powerful one, Brown et al (1981) has a probability of about 0.33 of detecting a threefold excess in liver cancer mortality), the lack of a latency relationship in that study and the complete absence of liver cancer in the other two studies strengthens this power in a way that cannot be quantified precisely.

The average duration of follow-up in each of the three studies was 15.3 years (Brown et al), 15.7 years (Maroni et al) and 20.2 years (Zack et al). Further follow-up, especially of the first two studies, would provide the longer latency and greater number of deaths that would increase the power of the studies. Nevertheless, the data available at the present time do not provide the consistent, exposure related results that would justify concluding that PCBs are carcinogenic in human beings.

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Table 1

Studies of Chloracne and Other Dermatitis in Relation to Blood PCB Levels*

Study	Chloracne	Other Dermatitis	Dose Related	Adjusted for Other variables
Fischbein et al (1979)	N	Y	Y	N
Baker et al (1980)	N	N		N
Maroni et al (1981 II)	Y	Y	?	N
Chase et al (1982)	Y	Y	?	N
Smith et al (1982)	N	Y	N	N

* N = Not found
Y = Found
No entry = Not reported
? = Equivocal finding

Table 2

Studies of Liver Function in Relation to Blood PCB Levels*

Study	Abnormalities	Dose Related	Adjusted for Covariables
Fischbein et al (1979)	N		N
Baker et al (1980)	N		N
Kreiss et al (1981)	N		Y
Maroni et al (1981 II)	Y	Y	N
Chase et al (1982)	Y	Y	Y
Smith et al (1982)	Y	Y	Y

* N = Not found
Y = Found
No entry = Not reported

Table 3

Studies of Fat Metabolism in Relation to Blood PCB Levels*

Study	Total Cholesterol	Triglycerides	Adjusted for Covariables
Fischbein et al (1979)	N	N	N
Baker et al (1980)	N	Y	N
Kreiss et al (1981)	Y	N	Y
Chase et al (1982)	N	Y	Y
Smith et al (1982)	N	N	Y

* N = Not found
Y = Found

Table 4

Inconsistencies in Mortality Studies of Cancer in PCB Exposed Populations

Study	No. Studied	No. of Deaths	Principal Findings
Brown et al, (1981)	2567	163	Liver Rectum
Bertazzi et al, (1981)	1310	27	Digestive Lymphatic and hematopoietic
Zack et al, (in preparation)	89	30	Lung

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