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Advances in Exposure, Health and Environmental Effects Studies of PCBs (Polychlorinated Biphenyls): Symposium Proceedings, May 12-13, 1982

Life Systems, Inc., Cleveland, OH

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Life Systems, Inc.

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ADVANCES IN EXPOSURE, HEALTH AND ENVIRONMENTAL EFFECTS STUDIES OF PCBs

SYMPOSIUM PROCEEDINGS

May 12-13, 1982

Prepared Under Contract No. 68-01-6554
Project 1247
ICAIR Work Assignment No.: 30

by

ICAIR
Life Systems, Inc.
Cleveland, OH 44122

for

Office of Toxic Substances
Health and Environmental Review Division
U.S. Environmental Protection Agency
Washington, DC 20460

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PCBs. These capillaries exhibited a bleed of 0.7 pA (flame ionization detection) at 320°C. The second method yielded thicker films (0.1 μ) for higher capacity for use with electron impact MS.

CONTENTS

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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).

Since 1978 there have been ten epidemiologic studies of the health effects of PCBs. Seven of them are cross-sectional investigations of symptoms and biochemical parameters. Of these, five are occupational, one is a study of both occupational and nonoccupational exposure, and one is nonoccupational. 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).

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 nonoccupational, 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 nonoccupational 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 versus 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

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

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 nonoccupational 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. 1981, 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.

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

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. (1981). 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. (1980) and Chase et al. (1982) 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.

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 musculoskeletal 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 gastrointestinal 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, anoraxia, 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. Nonstatistically 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 nonsignificant 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

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 hema-topoietic
Zack et al. (in preparation)	89	30	Lung

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 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 cliche 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 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

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 nonoccupational studies agree that there is no dermatitis associated with environmental, i.e., nonoccupational exposure. The difference in the results of the occupational and nonoccupational 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 nonoccupational 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 nonoccupational study did report an association.

The situation with respect to triglyceride levels is slightly more ambiguous. Two out of five studies, including one nonoccupational 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. (1981), 15.7 years (Maroni et al. 1981) 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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DISCUSSION SUMMARY

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Following the discourse of Dr. Gaffey, Dr. Philip Taylor presented preliminary results of a study he conducted in conjunction with investigators from the New York State Department of Health for the National Institute of Occupational Safety and Health. In this study, the effects of PCBs on reproduction in occupationally exposed women were investigated. This study was undertaken because in the Yusho episode (accidental ingestion of rice oil contaminated with PCBs, chlorinated dibenzofurans and quarterphenyls) 11 women were pregnant at the time of exposure, two of these women had miscarriages and nine had live births. Three of the infants were light for age and eight of the nine had various symptoms of fetotoxicity, such as eye discharge, cola-colored skin, and erupted teeth. In addition, fetotoxicity has been produced in a variety of animal species.

The cohort of women that was studied were workers for the General Electric Company at two facilities in Upstate New York south of Lake George. The two facilities were located in adjacent communities and have been involved in the manufacture of capacitors since 1946. There have been roughly 7400 individuals employed in those communities between 1945 and 1975, of whom about half were females. A cohort of women was studied whose personnel records indicated they had taken leave because of pregnancy.

Between 1958 and 1975, there were 388 pregnancies in 354 women that resulted in live births within the State of New York, and these became the object of the investigation. The information on birth weight, maternal age, parity, year of birth, race, sex, and date of last menstrual period was obtained from birth certificates, and where necessary hospital records and physician records were reviewed.

From a file of all single live births in the surrounding two-county area, a single control was selected for each of these births occurring to a capacitor worker matched on maternal age and parity precisely; year of birth plus or minus a couple of years; and race. The controls were cross-checked against the personnel files of the GE records to assure that they had never worked at GE. The cohort was limited to persons who had worked at least three months for GE and were divided into high and low exposure groups.

High exposure areas were those parts of the plant in which there was direct contact with PCBs during or after the introduction of PCBs into the capacitor. The areas of the plant with low exposure consisted of some women with clerical jobs which presumably would have no contact with the PCBs and women from the manufacturing process prior to the introduction of PCBs. In 1975, area samples taken in one survey showed that the values in the high areas, following the impregnation of PCBs were in the neighborhood of 679 ug/m^3 and in the lower areas they were 260. In 1977, the areas of high

furans (PCDFs) as of PCBs, in addition to polychlorinated quater-phenyls

exposure had an average value of 310 and the areas of low exposure of 227 $\mu g/m^3$.

Personal air samples were only done during a NIOSH industrial hygiene survey in the high areas and averaged 168 $\mu g/m^3$ air. Air samples taken immediately outside the plant averaged in the neighborhood of 6 $\mu g/m^3$ while ambient air levels are 0.1 $\mu g/m^3$ or less.

When the birth weights of infants from the low exposed group were compared to county controls, it was determined that the 337 infants of mothers in the low exposure group had birth weights that were 66 grams higher than the birth weights of the matched county controls. A comparison of gestational ages showed that the 51 neonates from high exposed women had a mean decrease of 3.4 days in gestational age and the mean difference of their birth weights was minus 95 grams when compared to county controls. This difference was not statistically significant.

However, when 51 neonates of high and 337 neonates of low exposed females within the plant were compared, the neonates of the high exposed group weighed an average of 153 grams less than the neonates of the low exposed group. This difference was statistically significant. When the data was adjusted for gestational age, it was found that the difference in weight was largely due to differences in gestational age. Overall, 13.7% of births occurred before 37 weeks of gestation in the high exposure groups and 5.6% in the low exposure group. The point estimate for the rate ratio was 2.4 with 90% confidence intervals that did not cover one. The meaning of these results, a reduction in gestational age of approximately one week and a reduction in birth weight of about 153 grams, when high and low exposure groups were compared within the plant is open to interpretation in terms of biological implications. This study was the only attempt to investigate reproductive outcomes in PCB exposed females.

All studies discussed by Dr. Gaffey in the presentation that preceded Dr. Taylor's were either cross-sectional studies in predominantly adult populations or mortality studies. Dr. Gaffey took the liberty of comparing studies that were basically quite different. Two of them were general population-type studies; the one by Baker, et al. of CDC, was done in Bloomington, Indiana. A general population that had been exposed to PCBs in soil was compared to a control population. This population had no higher blood levels of PCBs than the comparison group. It is therefore not surprising that no striking health effects could be associated with PCB exposure. The only exceptions were a small group of 18 workers or former workers who had had somewhat higher exposures.

Another study Dr. Gaffey mentioned was also a CDC study of a predominantly black population of the small town, Triana, Alabama. This population had had exceptional exposure to DDT residues, but in addition, when serum samples were analyzed, PCBs were also found in high concentrations in some of the people. A total of 458 people were examined, and the range of the PCBs in that group in serum was 3.2 to 157.9 $\mu g/l$. There were 98 persons in this group that had levels higher than 30 $\mu g/l$. There was no extensive PCB contamination in the town of Triana. The PCB blood levels in these people could be associated with the consumption of fish. As far as we could determine, the

fat PCB levels. Smith et al. (1982), in a study of 92 employees of two

PCB concentrations in fish had usually not exceeded FDA guidelines for the past ten years before the study was done. An additional important finding in this study was that as the age of the people increased, their PCB blood levels seemed to increase, and in females the PCB blood levels were lower than in males. According to a recent paper by Mary Wolff, there is also an increase in PCBs in adipose tissue with age. Dr. Chase in a recent publication, which was one of the papers reviewed by Dr. Gaffey, found that the workers with longer exposure had higher PCB body burdens.

The incidence of hypertension in this black population from Triana studied by Kreiss et al. was 30%. At a mean age of 24 years, this is a higher incidence than what has been reported among blacks. After adjusting for other confounding variables for hypertension, such as weight, cigarette smoking, age, alcohol consumption, there was still a small contribution which had to be attributed to PCB exposure. More studies need to be done to determine whether these findings can be verified. This population is quite different from the population that Dr. Blair Smith examined where no association with high blood pressure was found. In that population, the mean age was 40. Exposure was occupational in nature and most of the workers were white.

In addition, Dr. Gaffey discussed three mortality studies. All of them had in common that the number of available death certificates was very small. Even though small excesses of cancer were found, this information has to be taken with caution because of the limitations of the studies. Mortality needs to be examined further to determine what the significance of these findings is. If the latency period for the induction of cancer in humans is 20 to 40 years, a sufficient amount of time has not elapsed to determine whether exposure to PCBs is a risk factor in the development of cancer.

Although PCBs were first manufactured in the early part of this century, we are now beginning to see a larger population that has been exposed to PCBs for 10, 15, and 20 years or longer. This population will have to be followed further before any decision on the incidence of cancer in humans can be made.

Following these general comments, many different points were raised by the attendees.

Dr. Taylor was asked whether the children whose birth weight he reviewed were followed after birth. However, since his study was a record search study, this was not possible nor was it possible to control for confounding variables. It was, however, possible to establish that 11 children had died up to the age of 5. Seven of those deaths occurred among the 388 county controls and 4 occurred among the infants of the 377 low exposure group of the GE workers. In addition, it was again pointed out that the low exposed group and the high exposed group in the GE plant were not matched but adjustments for variables were made in the analysis of the data.

The point was made by Dr. Mary Wolff that Dr. Gaffey's statement about smoking among the workers of the Warsaw studies was irrelevant since the findings of restrictive pulmonary function tests made in that study were usually not associated with smoking. However, epoxies were used in that plant. This may be an important confounding variable.

Additional attempts to quantify exposure in the two GE plants studied by Dr. Taylor were made by Mary Wolff. The lower chlorinated biphenyls in people were strongly correlated with air levels while the higher chlorinated biphenyls were not.

Dr. Gaffey pointed out that the duration of followup in two mortality studies reviewed in his presentation (Brown and Bertazzi) was about 15-1/2 years and in the Zack study about 20 years.

So, the result is that the mortality rate, for example, in the Brown study for males was about 5.3 per 1000; in the Bertazzi study about 2.79; but among males Brown's rate was 3.8; Bertazzi's rate was 0.48. It seems to be an extraordinarily low mortality rate and yet it was almost 100% more than expected. It is very difficult to explain.

Zack's rate for males was 12.6 per 1000 which is understandable because the cutoff date for admission to the study was 12 years before the end of it, but it is puzzling. In the Bertazzi data the cohort is admittedly young. His males have a lower rate than Brown's, about half the rate, but his females have about 1/8 the rate. It is very puzzling to him.

Since in the Triana study (Kreiss, et al, 1981) exposure to PCBs and DDT residues had occurred, the question was raised whether the effects of DDT residues and PCBs could be additive, and it was pointed out that the analysis of the data did not seem to indicate this.

Dr. Blair Smith, National Institute for Occupational Safety and Health, indicated that in capacitor plant workers which he had studied the mean serum PCB levels of the lower chlorinated homologues were on the order of 500 µg/l with a background level of 10 to 15 µg/l. Yet, the mortality data from the Brown study of a plant which was similar were equivocal. He is therefore left in a quandry about trying to impute some human toxicity to PCBs in the occupational exposure situation.

In that regard Mr. David Brown asked him to say that he was planning to follow up on that cohort which has been followed through 1975. He will be following it through 1980. With additional years of followup, the study will statistically become more powerful and possibly some of the borderline excess risks for cancer may turn out to be statistically significant or possibly not. Dr. Smith went on to point out that in those studies where the magnitude of the association between PCB serum levels and biochemical tests was reported in a quantifiable way that the amount of variation was in general no more than about 10%. In regard to liver function tests and serum lipid or plasma lipid abnormalities, the associations appear weak.

When Dr. Smith analyzed his data obtained from capacitor workers blood pressure, unadjusted for age, was correlated with serum PCB level; but when it was age adjusted, the correlation went away. At present, it is not possible to explain the discrepancy between his study and that by Kreiss, et al. (1980).

Dr. Gaffey then made the point that the Brown and Jones' study has some data for longer latency periods, and the cancer data suggests no trend. He gave vinyl chloride as an example where, with these kinds of studies, some-

low chlorinated PCBs.

thing would have been seen. It was noted by Dr. Kimbrough that in the Brown and Jones study there seemed to be a trend for rectal cancer, and since vinyl chloride causes such an unusual tumor, it is much more easily detected. In addition, she pointed out that basically analyzing death certificates is a very insensitive tool.

Whereupon Dr. Taylor objected, indicating that relative to the other end points presented here, they are as sensitive. He also indicated that continuing as a former worker from CDC located in the New York State Health Department, he would be looking at and expected to have available information within the next year on the entire cohort of 7400 and some odd workers of the GE cohort. At this point, 750 deaths have been identified which will make the issue of arguing about thirties and forties reasonably moot for the particular PCB compounds that exposure was incurred at those particular facilities.

Dr. Gaffey in further commenting on the Brown study pointed out that there were only three liver cancer deaths; it is fairly difficult to show a trend with only three observations. The Brown study was, in terms of statistical power, a relatively weak study. It will become more powerful with increasing length of followup. As epidemiologists, we are dealing with highly variable outcomes fraught with error, both due to inherent biological variability and variability due to analytical technique and mediocrity of the recording of information on death certificates. Given the inherent dirtiness of the data, how refined does our measurement technique have to be in terms of separating out specific PCB isomers and homologues? In place of a single number, the proliferation of additional numbers as predictors is confusing.

Whereupon Dr. Taylor stressed that whenever randomly sloppy data are analyzed, the bias is always in the null direction. If a difference is demonstrated with sloppy data, it is more likely that it is true than it isn't. However, if a difference is not demonstrated and the data are sloppy, then it must be determined whether the inability to establish a difference is related to poor measurement techniques. Mr. Bob Noonan with Amtrak asked Dr. Gaffey whether, in trying to explain the apparent contradictions and inconsistencies in findings in the cross-sectional studies, was an attempt made to compare PCB dosage levels and mode of exposure. Dr. Gaffey stated that he did not attempt to do that.

Dr. Gaffey, when asked by Dr. Chase whether he felt that the studies he reviewed were not adequate stated that the cross-sectional studies were quite adequate and that the mortality studies are more adequate than has been suggested; and that the problems that have been raised about the power of the tests are beside the point because a complex of things is evaluated. The power is examined to detect excess mortality or a trend. In the studies that do not show an excess, it is determined whether there is something that is almost there, but there appears to be nothing of this kind. Maybe as these studies are followed up further, the evidence will become even stronger, but the evidence does not indicate a carcinogenicity problem with PCBs or other problems beyond the dermatitis and the marginal liver abnormalities.

According to Dr. Chase, when dealing with the issue of cancer with a long latency period exceeding the latency periods allowed for in any of the three cross-sectional studies, the studies were not sufficiently powerful, either

collectively or individually, to detect an increased risk. Further, there may not be a trend in the liver cancers, but there is an excess of liver cancers in the Brown study. The excess is conceded by Brown as not being statistically significant. It is of interest that there is an excess of liver cancer in the Yusho population as well, again, not statistically significant, and the conclusion is that a sufficiently powerful study is not yet available to say anything definite. This has been said by a couple of other speakers.

Dr. Gaffey responded that he did not mention the mortality in the Yusho population because he discounted it as a PCB-related phenomenon. It is not known out of what population it arose because as time has gone on, the definition of Yusho has changed, and the denominator has changed in ways that are not predictable. Secondly, the mortality data from the Yusho study have not been age adjusted. Thus it is not possible to determine what percentage is too high since comparisons with an age-adjusted population cannot be made. In other words, this is not an age and time-adjusted proportional mortality study; and third, the elapsed time interval, at least from the Yusho incident until the first mortality figures are given was ten years. For the Yusho deaths, the question is whether a latency period of less than ten years, may have been too short to cause the cancer. As far as Brown's study is concerned, even if his excess in liver cancer were statistically significant, it should not be accepted as being occupationally related unless it were related at the very minimum to latency of exposure and possibly also to duration, and neither of these were the case.

Dr. Chase agreed on the shortcomings of the Yusho data but the three studies presented by Dr. Gaffey do have some shortcomings as well. They are not adequate to draw a definitive conclusion as to the carcinogenic risk of PCB exposure yet. There is also a question about Fischbein's study. According to Table 2 of Dr. Gaffey's presentation, no dose relationship between liver function tests and PCB levels was found. The Fischbein article seemed to suggest to Dr. Chase that the main liver function tests were not significantly abnormal in the exposed group but that there was a statistically significant linear correlation between at least one of the liver function tests and PCB levels which has also been reported in other studies. Furthermore, in the 1979 Fischbein study it was stated that analysis of data to determine whether an association between PCB serum levels, cholesterol, and triglycerides existed would be reported at a later date.

Dr. John Brown of General Electric pointed out that chemically PCBs are lipophilic agents which tend to distribute at equal concentrations in all lipid pools in the body within a few days or weeks, and this means that the level in lipid reservoirs, such as the micellar lipids of the lipoproteins in blood tend to approach that of the PCB adipose tissue reservoirs. As a result, in any population of individuals having similar adipose tissue levels the blood level of PCB must of necessity parallel that of the level of blood lipid. So, there is a confounding in there. You predict that in a population of such individuals you would have to find a correlation unless the second law of thermodynamics were being violated. The correlation may become weak and difficult to see in a large population reflecting a large spread of adipose tissue PCB levels. The fact that there is a confounding between the levels of blood lipid and blood PCB means that it is difficult to establish correlations which infer that PCB has caused a change in lipid metabolism or a correlate of

elevated blood lipid such as hypertension. However, this does not mean that such hypothesized correlations cannot be tested. Instead, what it means is that the proper correlate to look for in testing either hypertension or serum lipid is not the serum PCB level but the adipose tissue PCB level.

In the case of the GE capacitor worker population, this has been explored by GE. A significant correlation of the serum PCB levels with both triglycerides and cholesterol was found. However, this correlation vanishes when correlations are made with adipose tissue PCB levels. Apparently Dr. Chase has made similar observations in his population and Dr. Brown raised the question whether this problem of confounding had been examined by others who are looking for abnormalities in lipid metabolism. It was pointed out by Dr. Kimbrough that to her knowledge, this had not been done. The fact that there are higher concentrations of lipids in serum might explain why some people have higher PCB blood levels. They were concerned about that in the Triana study because only blood levels were don.. In a population that gets older, cholesterol levels seem to increase in people that eat a western type diet and with it, PCB blood levels. One argument against that would be the fact that there seems to be a relatively consistent ratio between PCB blood levels and PCB adipose tissue levels.

Dr. Brown indicated that to the extent these ratios have been examined by GE, a better correlation exists between adipose tissue PCB level and serum PCB level if a correction is made for the serum lipid level.

In response to a question by Dr. Friess, Dr. Kimbrough stated that there are some scientists who feel that it would be better to use adipose tissue for the determination of body burdens and as an exposure index. It is of course more difficult to get adipose tissue than it is to obtain blood samples. In large studies, the tendency has been to use serum and to determine PCBs in serum and assume that this represents a small portion of what is in adipose tissue. If results from populations are reviewed where laboratory analyses have been adequate, there seems to be a constant ratio between PCB concentrations in adipose tissue and in serum. This ratio varies with time to last exposure if exposure was recent and such problems as weight loss.

Subsequently Dr. Ian Webber of RTE Corporation took issue with Dr. Gaffey's statement that the Yusho oil incident was not a PCB related incident. Dr. Webber stated that in the case of the Yusho oil the PCBs had been in use for some considerable time and had degraded to give a "dirty" oil. It might be that the heat exchanger application of PCBs results in a worst case situation. Transformer oils on the other hand tend to degrade also. From a practical point of view, health studies that involve the largest amount of exposure to people in terms of either those getting rid of PCBs from contaminated oils or people involved with retrofilling transformers, should be done because these are the people who are likely to come into contact with dibenzofurans in PCB solutions. Have any studies been done with used PCBs?

Dr. Robert Bell from GE then informed the audience that they were in the middle of a project evaluating 40-year-old transformer fluid. Their findings to date indicate that the levels of dibenzofurans in 40-year-old fluid are at or below levels of the original PCBs that were delivered to GE. Thus, transformers operating at ambient temperatures do not pose a significant hazard.

Dr. Webber countered that those transformers operating at ambient temperature probably do not contain significant levels of dibenzofurans. There are however, a lot of factors in the use of PCB oils that come into play, the age, the amount of oxygen involved and hot spots caused by faulting.

Dr. Bell then mentioned the Binghamton case. Dr. Kimbrough asked whether everybody was familiar with the Binghamton situation. A transformer caught fire and a lot of combustion products were formed. Because the transformer also contained chlorinated benzenes, chlorinated dibenzodioxins formed in addition to chlorinated dibenzofurans, and because of the way the airshaft was situated in relation to the transformer, all of this material was evenly distributed over a very large state office building.

According to Dr. Ahmed, epidemiology is a two-edged sword and one can pretty much argue one's case depending upon how one interprets the data. Taking Dr. Gaffey's presentation and other information as well, a correlation is assumed between PCB blood concentration and actual exposure levels. In any kind of an epidemiologic study, it could be asked what the actual exposure level of the individual or cohort to a given agent was. Obviously, surrogates are used, and this could lead to all kinds of interpretations which may lead to positive correlations or negative correlations depending upon how it all comes out.

Secondly, to address the problem of confounding variables, Dr. Gaffey in one slide showed studies that were done since 1978. Some of the studies had been adjusted for confounding variables, and some of them had not. Dr. Kimbrough's data showed that PCB blood levels increase with age, at least in this particular group and that there was a sex difference in PCB blood level. This alone should warn us that we should try to adjust for variables in any of these studies. We have to adjust for age, ethnic differences, sex, and so on. Unless this is done for all studies, they cannot be compared on the same basis. Those studies that do take smoking habits and various other confounding variables into account are obviously far better. Unfortunately, many of the studies presented here have not looked into these factors properly. Dr. Gaffey made a suggestion that statistical power could be increased if studies were combined. Issue must be taken with pooling different populations from different geographical areas, such as the Brown study and the Bertazzi studies, which were done in two different parts of the world. The two populations obviously had ethnic differences and the study protocols used were quite different. Statistical power, even though we should look at all of the information in a qualitative way, has to be used in such a way that the statistician will agree gives a value of the sensitivity of the study. Some of the studies presented today were occupational and others nonoccupational. No information was given in the nonoccupational studies about the degree to which these individuals were exposed. Problems about latency periods exist. Since when and how long were individuals exposed to PCBs? How did their blood concentration correlate with their actual exposure years ago? There are so many problems with each of these studies, it cannot possibly be concluded whether or not PCBs cause the kinds of problems presented. We do have positive studies on dermatitis and chloracne. Then there are studies that conflict with one another. How can it be concluded that this means that there are no problems associated with PCBs?

Dr. Gaffey responded that he did not think that he said there were no problems, but that he specified the problems that seemed to be consistently turning up. In addition, there is almost no way to get around using surrogates for exposure in cohort mortality studies because it is not possible to measure with any precision the exposures that took place many years ago. Furthermore, confounding variables can frequently create spurious differences. They can rarely wipe out real differences because to create a difference where there, in fact, is none, any confounding variable will do. But to wipe out differences that exist, a conspiracy among a number of confounding variables is needed which is rather unlikely. The nonoccupational studies have in common the fact that their exposures are low, and the occupational studies have in common the fact that their exposures are high. It was not suggested that some simple piece of arithmetic can combine all these studies into one overall numerical estimate of power, but any reasonable assessment of the evidence has to regard not the power of an individual study, but the mass of the evidence, not necessarily in any formal way, although this could be done.

Dr. Kimbrough pointed out that individual susceptibility must be considered as well and that there seems to be an effect on reproduction in animals and that has not been studied to any great extent in humans. Animal data also suggest that females are perhaps more sensitive to the toxic effects of PCBs than males, and perhaps a greater effort should be made to look for health effects in females.

Dr. Brown responded to an earlier question raised by both Dr. Friess and Dr. Ahmed relating to the persistence of PCBs in the body and whether body burdens can be used as a measure of integrated exposure. They are attempting to answer this question through their studies of the GE capacitor worker group. The results to date indicate that most PCB isomers of the Aroclor 1254 type are highly persistent in the body, and they don't clear. Once they have been deposited in the body they are there forever unless they can be excreted through lactation. This may be true for a few isomers of the lower PCBs. There may be one or two isomers that can be used for tracking integrated exposure. This is not certain yet. Most of the lower chlorinated homologues are cleared but certainly the higher isomers represent a permanent record of exposure.

CHAPTER 6

HEALTH EFFECTS - LABORATORY STUDIES

The first paper in this chapter reviews the designs and results of animal studies performed to assess the toxicological effects of PCBs. For the sake of thoroughness, this review includes several studies completed prior to 1978. Data are presented and discussed on the following topics: skin effects, reproductive dysfunction, teratogenicity, fetotoxicity, liver structural and enzymatic alterations, gastric lesions, immunosuppressive effects, porphyria induction, carcinogenesis, and mutagenesis. The paper concludes with a summary of known effects in animals and a comparison of these to findings in humans.

The second deals specifically with one PCBs effect known to occur in both animals and humans -- liver enzyme induction. The data demonstrates in substantial detail how substitutions in the para, meta, and ortho positions can alter this activity. The enzyme induction by the PCBs is compared to the established structure-activity relationships of the phenobarbital and methylcholanthrene type inducers, as well as to the more hazardous polychlorodibenzo-p-dioxin compounds.

The discussion summary begins with a detailed analysis of the animal carcinogenicity studies, both those presented in the paper and several additional studies. The discussion summary then examines the "initiator-promoter" theory and the implications of rat liver nodules findings.