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 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).

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.

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, 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

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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General Comments

These documents are somewhat unobjectively written with unscientific discussions such as:

On page 3-23 the author states: "However, the overzealous use of mathematical models and the assumptions made by the EPA without comparing these results to reality are easily demonstrated."

The report by the New England Gas Association begins "The discovery of small amounts of PCBs, the use of which has been banned by the EPA, in natural gas transmission lines is neither unexpected nor cause for public alarm."

Later in discussing acute PCB toxicity the report states: "Short term effects of moderate doses in animals are minimal. The toxicity is comparable to that expected from such substances considered relatively safe such as table salt, alcohol or caffeine."

In discussing chronic effects the report states: "...PCBs produce minimal changes in new borns. In fact they are no more toxic to the fetus than most chemicals, and less toxic with regard to birth defects than some common vitamins and hormones."

Summary of the Health Effects of PCBs

The "Summary of the Health Effects of PCBs" tends to misguide the reader as to what the actual articles present. The overall tone of the Summary is a refutation of the technical presentation or an exaggeration of the "negative" arguments presented in the six review articles.

On pp. 1, 2-1, and 2-2 of the Summary, the authors cite and discuss Weisburger's and William's concept of promoters and initiators, and epigenetic and genotoxic mechanisms. However, they do not point out that the concept and the classification of carcinogens by Weisburger and Willaim are not shared by many.

On pp. 1, 2, and 1-5 the authors discuss the large number of negative carcinogenicity studies for PCBs and present the inadequacies of the positive studies. They do not mention the inadequacies of the negative studies. For example, the reference papers show that only a few of the negative studies are of sufficient duration to adequately characterize them as negative studies. Most of the studies quoted in the six articles are of one year or less duration (e.g., see article by Crump, p. 24). For the positive studies, they criticize that the length of exposure was too short for an adequate study design (p. 3-3). This is not a relevant concern for a positive study.

The authors also stated that the positive studies should be discounted because of inadequate design. If this is the case, the negative studies should also be discounted as well. It is far more difficult to prove a negative result than a positive one.

Often, observations cited in the review papers are neglected or omitted in the CMA Summary. For example, p. 3, paragraph 2, sentence 3 of Summary: "The preponderance of studies has not identified a clinical disease associated with exposure to PCB, nor has it provided persuasive evidence of health impairment" compared to Paper No. 1, p. 22, paragraph 1, last sentance: "...a single study which suggests that diastolic blood pressure may be related to blood levels of PCBs." This study suggests some cardiovascular toxicity. In addition, dermatologic reactions is known to be associated with PCBs poisoning.

The Summary contains too much emphasis on the possible carcinogenicity of PCBs and does not mention much on the possible chronic health effects. The six articles have more details of the chronic effects.

One of the controversial issues in this document is that the CMA contractor feels that PCBs are tumor promoters and not initiators. Since promoters may have threshold and reversible effects, the authors feel that low level exposures do not represent a hazard for cancer. The evidence for this assertion is presented on page 2-7 through 2-8 and again on pages 3-17 through 3-19. These arguments can be summarized as follows.

1) PCBs increase the frequency of liver tumors in rodents; a tumor type which occurs spontaneously in these animals.

2) PCB induced tumors are not metastatic.

3) PCB tumors are not transplantable.

4) Promoters are not mutagens. Many of the mutagenicity test on PCBs were negative.

5) Continued presence of PCBs is required to sustain liver neoplasia and removal may cause tumor regression.

There are several problems with this line of reasoning. First the mechanisms of action of initiators and promoters are becoming less clear. The dogma that initiators cause mutations and promotors have "epigenetic" effects in cancer expression is no longer totally accepted. Cairns has recently proposed that initiators may not act through the induction of mutations by way of DNA damage as is usually thought. Further, the term epigenetic is not very useful; for example, what if a chemical caused a heritable change in chromatin structure by altering the action of DNA methylases. This affects the DNA and therefore is

"genetic," and yet neither the sequence of bases nor the number of chromosomes is affected. Because of such difficulties it is better, perhaps, not to stereotype chemicals.

Even if we accept the contractors reasoning, it is important to note that not all mutagenicity tests on PCBs were negative. In the Monsanto document entitled "A review and evaluation of carcinogenicity in mice and rats and mutagenicity studies with PCB" several positive mutagenicity tests were cited along with the negative results: Aroclor 1221 and 4-chlorobiphenyl were positive in the Ames test. TCB and the 3, 4 epoxide of TCB induced single strand breaks in DNA of L-929 cells. Kanechlor 300 was found to induce chromosomal aberrations in vitro while Kanechlor 500 was positive in vivo. Continuous exposure of C3H 10T ½ cells to Aroclor 1254 caused cell transformation to type III foci. These cells formed a sarcoma when implanted into irradiated mice. Aroclor 1260 and 2,4,5,2',4',5' hexachlorobiphenyl also caused morphological transformation of C3H 10T ½ cells. 4-Chlorobiphenyl caused an increase in unscheduled DNA synthesis in CHO cells while Aroclor 1254 induced chromosome damage in ring doves fed a 10 ppm diet. Clearly, based on these data one can argue that PCBs may have initiator activity.

Finally, in calculating the risk estimate for increased human cancer cases caused by exposure to PCBs, the contractor made (but did not state) an enormous assumption. It was assumed that because hepatomas were induced in rodents, this was the only tumor type for which humans were at risk. Although the correlation between carcinogenicity in animals and man is good, the issue of site concordance is not clear. Therefore, humans may be at risk for other types of tumors as well. Since the incidence of hepatomas in the human population is low, the risk estimate produces a very low number of PCB induced cancer. However, if these chemicals were also associated with lung carcinoma, for example, risk estimates would be much higher.

The latter part of the Summary consists mostly of a complete refutation of the risk assessment done by Crump and Masterman, the last document on the "Assessment of Carcinogenic Risks from PCBs in Food," with very little documentation of the reasons for not accepting Dr. Crump's assessment. In his assessment, certain models are used to derive virtually safe doses of PCBs at specified risks. He includes the probit model, the one-hit model, and the multi-stage model. He also uses the one-hit and multi-hit models to derive estimates of life time extra risks to humans for certain subpopulations at risk. Although the "Summary" is interesting reading, in most cases it is not of sufficient scientific validity to warrant a response. In any case, the Summary conclusions for risk assessment are not supported by the technical review documents. In fact, unlike the other section such as epidemiology, the risk assessment section

does not even attempt to summarize the material in the risk assessment technical document. There are several specific problems with the Summary.

1) Several places in the Summary (pages 4-5 and 1-3) the authors conclude that there is little reproductive risk from PCBs in animals. The Crump and Masterman document contains the data from the reproductive studies in monkeys which showed effects at levels as low as 2.5 ppm. The PCB data is unusual in showing reproductive effects at levels lower than those at which carcinogenic effects are seen. The fact that this is not even mentioned in the summary document, even though one of their own technical review documents include the data, casts some suspicion in the summary document.

2) Aside from the biological arguments regarding mechanism of cancer which are used to refute Crump's risk assessment, there is another major argument proposed. It is that if the risks are as large as Crump's estimates indicate, these risks would have been detected by now in high risk populations. The review of the epidemiology studies show the highest number of cohort deaths studied for sufficient latency periods is less than 100. It is doubtful that relative risks of less than 15-20 times would be detected with this size population (we are presently doing the calculation).

3) Using the EPA Water Criteria documents, the authors in the summary section calculated the expected increase over background cancer for certain subpopulations. There is a mistake somewhere in the conversion figure given in Table 3-5 equating 79 ng/l to 80 ug/day. The 80 ug/day does not produce the expected increases over background shown in Table 3-6. A conversion to 80 ng/day rather than 80 ug/day would produce the estimates shown in Table 3-6 and on pages 4-10 the figure is given as 80 ng/day.

4) On pages 4-6, the authors use the CAG documents which show that if PCBs are not carcinogenic, the allowable daily intake would be 210 ug of PCBs per day. This is calculated using reproductive data in minks (which was similar to reproductive data in monkeys) and a safety factor of 100. This allowable daily intake of 210 ug/day is not disputed by the authors, yet the exposures shown in the table on page 4-11 for capacitor workers is 4 times higher than this allowable daily intake. Therefore, even without considering carcinogenicity, the allowable daily intake of 210 ug/day, which is used by the authors to question the much lower safe levels from cancer data, is already 4 times lower than average exposure of capacitor workers. All the arguments used in the Summary for negating certain models used for extrapolation of cancer risks by mechanistic arguments would have no relevance to reproductive data.

5) The authors of the summary document makes no attempt to estimate any risks according to their proposed model of cancer. This may be because the probit model, also used by Crump, gives the lowest risks of almost any model available at low levels. The safe levels shown on page 34 of Crump's report using this model are below the exposure of average capacitor workers, even for risks as high as 10^{-3}.

The Epidemiology of PCBs

The Epidemiology of PCBs by Gaffey was reviewed in great detail. Our comments are directed to answer the question of whether his conclusions and generalizations are justified based on our cursory review of the cited studies. We chose to begin with the review of the carcinogenicity section since this is of most concern.

Carcinogenicity: In general, Gaffey's conclusions concerning the strength of epidemiologic evidence necessary to support a causal association between PCB exposure and carcinogenicity are reasonable in light of the criteria established in Richard Doll's paper. However, several of the studies reviewed by Gaffey (Bertazzi et al, Zack and Musch) suggest an overall increase in risk from death due to cancer and all studies reviewed by Gaffey do in fact reveal excesses for specific sites; although most of these excesses were not statistically significant or site concordant with one another. It should be stated at the outset, that the presence of consistency strongly supports causality, but its absence does not rule it out.

Gaffey deliberately omitted the preliminary mortality findings of the Yusho incident from this section because this study was not an epidemiologic analysis directed at cancer. Urabe et al reported 11 deaths from malignant neoplasms among 35 confirmed deaths of Yusho victims. The authors state that "this rate (11/35) is substantially higher than the 21.1% that is the mortality rate from neoplasms in the same prefecture" for that year (1977) but the authors also state that "it would be premature to conclude that this high mortality bears association with PCB poisoning." Nevertheless, three of these deaths were due to liver cancer and two from lung cancer, which suggests some concordance with reports from previous studies (Zack and Musch, Brown and Jones).

Several of the studies reviewed by Gaffey (Bahn et al, Zack and Musch) are based on so few deaths, especially among those workers with ten or more years of exposure or 15 years since first exposure, that it would be premature to conclude that PCBs are definitely non-carcinogenic. For instance, in the one study (Brown and Jones) with the greatest number of person-years observed, there were 183 deaths and it is not clear how many of these deaths were among workers with five or more years of exposure or 15 years latency since first exposure to PCBs.

Furthermore, the power of detecting a significant elevated risk has not been reported for any of these studies and these calculations should be performed as part of our in-depth review.

In addition, it should be noted that most of the studies reviewed by Gaffey are mortality studies, and not incidence studies, and are therefore based on death certificate information which is known to have certain limitations for detecting cancer risks due to chemical exposure. The principal limitation being that analyses based on deaths alone may exclude those workers who left employment from a study plant and later developed cancer, but have not expired and are therefore not counted among the cancer deaths.

With the exception of the Yusho study (Urabe et al), no reliable data on past industrial exposure were reported. Two studies (Brown and Jones; Bertazzi et al) reported relatively low airborne levels of PCBs as estimates of current exposure. Only Bahn et al reported that their study population were "believed to have been heavily exposed" to PCBs. In the absence of high body burden levels or clinical indications of chloracne, we would have to assume that occupational exposure to PCBs was relatively low, and, therefore, would not be expected to produce a measurable differential effect on mortality.

In summary, based on the preliminary results reported in the literature, Gaffey's conclusions with respect to cancer risk seem reasonable, but he unjustifiably dismisses the significance of suggestive evidence. Bertazzi et al, for instance, recognizing the limitations of their analysis based on a few number of deaths (27), state that "the results so far obtained are strongly suggestive of an excess of mortality from cancer among male workers and an excess of mortality from all causes and from cancer among female workers." Several of the studies reviewed by Gaffey (Brown and Jones, Bertazzi et al, Zack and Musch) determined the vital status of their cohorts as of 1977 and 1978. It is possible that formal requests to these investigators to follow-up their investigations through 1981 may resolve ambiguities that are due to insufficient numbers of deaths.

Finally, Gaffey reports on the private communication of preliminary results from two investigators (Rousch and Sinclair) whose results should be secured as soon as possible so that we can evaluate their relevance to Gaffey's conclusions. It is our opinion that further rigorous evaluation by more qualified experts is inherently desirable and will add to our understanding of the significance and deficiency of these studies, but we doubt that there is sufficient epidemiological evidence at this time to support a causal association between PCB exposure and cancer. Additional studies among more highly exposed workers with sufficient numbers of deaths should be supported in order to resolve reasonable concerns about the potential carcinogenicity of PCBs.

Accidental Heavy Exposure: Gaffey reviews two incidents in this section (Meigs et al, Yusho reports), but Meigs is more appropriately reviewed in the next section.

The numerous studies which have been published in conjunction with the Yusho incident represent a sizeable fraction of the total health effect literature concerning PCBs. Gaffey, and the authors of the General Electric health effect report, attempt to minimize the relevance of these findings for two main reasons: (1) samples of the Kaneni Rice Oil were found to be contaminated with dibenzofurans, and (2) victims of this incident ingested large doses of PCBs which are irrelevant to assessing the health effects from lower occupational exposures found in the United States. Proper evaluation and interpretation of these objections are crucial to the assessment of health effects related to PCB exposure.

Yusho disease is a Japanese term which refers specifically to acute and sub-acute poisoning due to ingestion of Kaneni Rice Oil which was contaminated with PCBs. There seems to be a general consensus that the average amount of Kanechlor ingested was estimated to be about 2 gm while the minimum amount ingested by a patient was about 0.5 gm. As of 1977, there were 1,665 victims of Yusho, who exhibited a variety of acute symptoms ranging from severe chloracne and hyperpigmentation to less specific effects such as vomiting and diarrhea.

The most notable finding from this incident seems to be that patients seen three and six years after first coming down with Yusho disease still exhibited symptoms of Yusho, biochemical abnormalities and persistent blood levels of PCBs. Unless these effects can all reasonably be attributable to the dibenzofuran contamination, then I would say that the severity, incidence and persistence of these effects all warrant serious concern for PCB exposure. Both the specific toxic effects (as determined from animal and human studies) of PCDFs and PCBs must be compared, as well as the quantitative evidence supporting the extent of PCDF contamination.

With respect to the preliminary mortality reports, Gaffey justifiably calls attention to the problem that the population-at-risk, or denominator of the relative risk rates, cannot be determined, and therefore presents a problem for determining the actual "attack rate" as well as the relevance of elevated cancer deaths among Yusho victims. This problem is mitigated somewhat by the finding that among a group of 146 known users of oil, 80 consumed less that 720 ml, and 88 percent of these users were affected. Among those who used more than 720 ml, 100 percent were affected. This would suggest that Yusho victims, as defined by various clinical criteria, do in fact represent the total number of people exposed to contaminated oil. This, of course, is conjecture and is subject to much criticism. But until this problem is resolved, epidemiologic analyses utilyzing the cohort approach may be inappropriate and unacceptable.

Gaffey only briefly reviews the reproductive effects seen among children of Yusho victims and he neglects entirely to report on more recent findings. The EPA Water Quality Criteria document reports that "thirteen women, 11 with Yusho and 2 without, but married to men with Yusho, delivered 10 live and 2 stillborn infants between February 15 and December 31, 1968." Nine of the 10 had hyperpigmentation, and 5 had grayish-dark pigmentation of the gingiva and nails. Other findings of reduced growth, prematurely erupted teeth and increased eye discharge were also reported. Nine more infants with hyperpigmentation were born to Yusho mothers between 1969 and 1972 (Yoshimura 1974). The Water Quality Criteria document reports on several studies which found elevated levels of PCBs in breast milk of Yusho women. Again, the significance of these findings depends upon our interpretation of the relevance of PCDF contamination, as well as on the potential for lactating mothers with high body burden levels to deliver PCBs to nursed infants.

Environmental Levels and Body Burdens: Gaffey's conclusions seem reasonable and justified. He concludes that high exposure to PCBs results in higher body burdens, all other things being equal. There were a few inconsistencies which can be adequately explained by more rigorous interpretation of the studies which will have to be addressed in a more in-depth review. Specifically, what is the significance of high burden levels? Is there a threshold level for adverse health effects? What is the significance of higher chlorinated compounds and what is the potential for future bioaccumulation under current exposure situations?

Epidemiologic Studies of PCBs and Health: Dermatologic effects: Gaffey justifiably concludes that "the data suggest strongly that when PCB blood levels exceed about 150-200 ppb, chloracne can occur," but most studies have shown that the occurrence of chloracne is not further associated with blood PCB levels." Gaffey suggests that this apparent inconsistency may be a function of personal idiosyncratic factors or that not all cases of high blood PCB levels are associated with chloracne because they do not have sufficient skin contact for chloracne to develop. In any event, dermatologic reactions have been consistently associated with PCB exposure and these reactions can occur under occupational exposure conditions as low as 0.1 mg/m^3.

Liver function: It is difficult to make any interpretation of these findings without reviewing each of the nine studies. In general, there does not seem to be consistent findings of abnormal liver function or biochemical indicators of enzyme activity; nevertheless, several studies did report abnormalities in enzyme levels which may have relevance beyond that suggested by Gaffey.

Fat metabolism: Gaffey's conclusions as stated are consistent with the reported findings.

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"Most studies, including one non-occupational study have associated increased tripycerides with PCB exposure. The data on cholesterol are not consistent; an increase, a decrease and no change were found (one study each). HDL cholesterol either decreased or was unchanged (one study each). Even if PCB exposure has some effect on fat metabolism, it appears to be without any apparent clinical significance."

Symptoms, Illness and Other Conditions: All of the studies reviewed in this section should be more thoroughly evaluated. Gaffey quotes Smith et al. as saying "that no studies to date have shown that occupational exposure to PCBs is associated with any adverse health outcome, to be distinguished from demonstrable subclinical biochemical alterations." It is possible that these biochemical abnormalities have not yet revealed any clinical manifestations, and it is not clear whether the subclinical alterations present serious health effect concerns.

In general, most of these studies are cross-sectional, and therefore make no effort to ascertain the true population-at-risk. In other words, the investigators did not identify their study populations from historical employment records - thereby ensuring that all workers had some minimal duration of exposure - and furthermore, these studies made no effort to identify workers who may have left employment for occupational health reasons. In most cases, the study population represented those workers currently employed and healthy.