OCCUPATIONAL EXPOSURE TO PCBs AND VARIOUS CANCERS

Report by the
Industrial Disease Standards Panel

IDSP Report No. 2

December, 1987

COMMENTS

by the

NATIONAL ELECTRICAL MANUFACTURERS ASSOCIATION

WASHINGTON, D.C. USA

March, 1988

National Electrical Manufacturers Association
2101 L Street N.W., Suite 300
Washington, D.C. 20037 (202) 457-8400

Daniel K. Shipp
Vice President
Public Affairs

March 8, 1988

Dr. Robert G. Elgie
Chairman
Workers' Compensation Board
2 Bloor Street East, 20th Floor
Toronto, Ontario
Canada M4W 3C3

Dear Dr. Elgie:

The National Electrical Manufacturers Association (NEMA) submits comments in this letter on the Report to the Workers' Compensation Board on Occupational Exposure to PCBs and Various Cancers prepared by the Industrial Disease Standards Panel (IDSP Report No. 2) dated December, 1987. NEMA, which represents manufacturers of electrical equipment such as transformers and capacitors, has had a long and very close involvement with PCBs even pre-dating enactment of the Toxic Substances Control Act (TSCA) in the United States which specifically banned further manufacture of PCBs and is gradually phasing out their continued use.

NEMA also has a close association with the Electrical and Electronic Manufacturers Association of Canada (EEMAC) with several manufacturers having production facilities in both countries.

In making these comments, we have drawn upon our own extensive experience and knowledge of the health effects of PCBs. In addition we have asked Dr. Jack S. Mandel of the University of Minnesota to provide an objective scientific review of the IDSP report. The review of Dr. Mandel and his associates is attached and forms the basis for our comments.

We believe that the large body of toxicologic and epidemiologic data does not justify findings of the Panel that there is a "probable connection between liver, biliary tract and gall bladder cancers and occupational exposure to PCBs." To the contrary, we believe the evidence does not support this finding.

Animal Studies

The review of the animal studies by the Panel is not complete and does not include a balanced perspective on the studies. Studies showing an increase in liver carcinoma did not show an increase in total tumor incidence, in fact, some show a decrease in the non-liver carcinomas. In two of the studies mortality among the PCB exposed animals was actually decreased.

The studies do not "demonstrate reasonable consistency" as stated in the Panel's report. The studies are inconsistent, and part of this inconsistency possibly stems from comparing the carcinogenicity of the different commercial PCB mixtures. Results show an association between fairly large doses of only the most highly chlorinated (e.g. Kanechlor 500 or Aroclor 1260) PCB compounds and site-specific (liver) tumors. The effect appears to be species-specific (primarily in rats).

Extrapolation of the isolated findings in animals to humans is tenuous at best.

Epidemiology Studies

We do not believe the Bradford Hill criteria to assess the causal significance of an association are met. Contrary to claims in the Panel report, association is neither strong nor consistent. The strength of the association is substantially reduced if a two-tailed test is used, if an adjustment is made for multiple hypotheses testing, if only liver cancers are considered and the effect of confounding factors is removed. Consistency is not demonstrated since the individual studies do not all show a significant association. No dose-response relationship has been demonstrated.

None of the individual human mortality studies presented by the Panel shows a significant association. The authors of these reports conclude that no association has been demonstrated. None of these studies accounted for confounding factors such as alcohol use, hepatitis infection, or use of oral contraceptives, known risk factor for liver cancer.

All the studies lumped together cancers of the liver, biliary tract and gall bladder even though the animal studies dealt primarily with liver cancer. Of the seven cancers of the liver, biliary tract or gall bladder considered to be significant, four people had a duration of employment of one year or less, three were not confirmed and only two were classified on the death certificate as primary liver cancer. Three of the seven cancer cases occurred in one plant (Massachusetts) in one study (Brown and Jones). None of these was a primary cancer of the liver. Two of the three cases worked 1.5 years or less.

The use of a meta-analysis to sum the observed and expected results from the "five" studies is questionable because of the substantial dissimilarities among the studies. Such aggregated analyses have been used to date only with randomized controlled trials.

In summary, we do not agree with the finding of the Panel of a "probable connection between liver, biliary tract and gall bladder cancers and occupational exposure to PCBs". Based upon our analysis of the data presented in the IDSP Report, we are convinced that the evidence is not strong and the association cannot be considered causal. "Strong" and "causal" are used to describe associations such as those between cigarette smoking and lung cancer or asbestos and mesothelioma where the data are consistent and persuasive. To use these words to characterize the association between liver cancer and PCB exposure is to distort and grossly exaggerate the weak and inconsistent data that are available.

We appreciate the opportunity to submit these comments to the Workers' Compensation Board of Ontario and trust that they will be given fair consideration. Please feel free to contact either me or Dr. Mandel directly should you need clarification of our remarks. We are also very willing to come to Toronto to discuss our review with the Board.

Very truly yours,

D K Shaffner

DGB/bs

cc: Ms. Linda Angove,
Acting Secretary of the Board

A Review of

"Report to the Workers Compensation Board
on Occupational Exposures to PCBs and
Various Cancers"
IOSP Report No. 2

Submitted by

Jack S. Mandel, Ph.D., M.P.H., Allen Williams, M.A., M.P.H.
and Pat Coin, Ph.D. (cand.)

March 1, 1988

Summary

Animal Studies

1. The review of the animal studies by the Panel is not complete and does not include a balanced perspective on the studies.

2. The results from the animal studies show an association between fairly large doses of only the most highly chlorinated (e.g. Kanechlor 500 or Aroclor 1260) PCB compounds and site-specific (liver) tumors. The effect appears to be species-specific (primarily in rats).

3. Extrapolation of the isolated findings in animals to humans is tenuous at best.

Human Mortality Studies

4. None of the individual human mortality studies presented by the Panel shows a significant association. The authors of these reports conclude that no association has been demonstrated.

5. None of these studies accounted for confounding factors such as alcohol use, hepatitis infection, or use of oral contraceptives, known risk factors for liver cancer.

6. All the studies lumped together cancers of the liver, biliary tract and gallbladder even though the animal studies dealt primarily with liver cancer.

7. The use of a meta-analysis to sum the observed and expected results from the "five" studies is questionnable because of the substantial dissimilarities among the studies.

8. The use of a one-tailed statistical significance test is not appropriate.

9. No account was made for the fact that 21 tests were conducted to determine significance. Chance alone would result in the significance of one SMR. An adjustment to the p value should be made for multiple hypotheses testing.

10. Of the 7 cancers of the liver, biliary tract or gallbladder considered to be significant, 4 had a duration of employment of one year or less, 3 were not confirmed and only 2 were classified on the death certificate as primary liver cancer.

11. No dose-response effect was demonstrated.

12. Three of the 7 cancer cases occurred in one plant (Massachusetts) in one study (Brown and Jones). None of these was a primary cancer of the liver. Two of the 3 cases worked 1.5 years or less.

13. The Bradford-Hill criteria to assess the causal significance of an association are not met. The strength of the association is substantially reduced if a two-tailed test is used, if an adjustment is made for multiple hypotheses testing, if only liver cancers are considered and the effect of confounding factors is removed. Consistency is not demonstrated since the individual studies do not all show a significant association. No dose-response relationship has been demonstrated.

Review of "Report to the Workers Compensation Board on Occupational Exposure to PCBs and Various Cancers" IDSP Report No. 2

Introduction

In December 1987, the Industrial Disease Standards Panel of the Ontario Ministry of Labor submitted to the Workers' Compensation Board a report on occupational exposure to polychlorinated biphenyls (PCBs) and cancers. This report was in response to a request from the Workers' Compensation Board to consider the issue of the human carcinogenicity of PCBs for purposes of determining entitlement for workers occupationally exposed to PCBs who have developed cancer. The basis of the Panel's recommendations is the "Report of the Special Panel on Occupational PCB Exposure and Various Cancers: Human Health Effects and Carcinogenic Risk Potential of PCBs". This Special Panel, chaired by Dr. William Nicholson of the Mount Sinai School of Medicine, New York, reviewed the experimental animal studies and observational human studies and conducted a meta-analysis of the epidemiologic mortality studies to reach the conclusion that there is, "a probable connection between liver, biliary tract and gallbladder cancers and occupational exposure to PCBs". Following is a critical review of the Special Panel's report.

Experimental Animal Studies

Although the Special Panel does not explicitly define the scope of, or approach to, the review of the experimental PCB literature, it appears that the Panel sought to provide a somewhat broad and general overview of this literature, as opposed to a comprehensive and critical review. The Panel

cites most, but not all, of the major animal studies cited by other reviewers. Furthermore, they do not discuss all the important findings in the studies that they review.

The first study cited on PCB-induced liver cancer was that of Ito et al., 1973, who fed male mice a diet of 100, 250, or 500 ppm of Kanechlor 300, Kanechlor 400, or Kanechlor 500. Neoplastic nodules and hepatocellular carcinomas were seen after 32 weeks only in the group exposed to 500 ppm of Kanechlor 500. Seven of 12 animals were found to have neoplastic nodules and 5 of 12 hepatocellular carcinomas. It should be noted that the effect was observed only in the mice fed the diet with the greatest (500 ppm) dose and most chlorinated (54%) PCB compound. The second study of mice (Kimbrough and Linder, 1974) found evidence of nonmalignant lesions in 47% of the mice after an 11 month diet of 300 ppm of Aroclor 1254.

Six studies on rats were reviewed in the Special Panel's report. The first (Kimura and Baba, 1973) found neoplastic nodules in only female rats fed over 1200 mg of PCB in their diet. No mention is made of the second study by Kimura et al. in 1976 which did not find an association between hepatocellular carcinoma and PCBs. The Panel concluded that the study by Ito et al. in 1974 demonstrated that, "all three Kanechlors produced liver changes related to the concentration in the diet." Table 3, presented in support of this statement, contains data on the histopathological findings in the liver of rats given PCBs. At the highest dose (1000 ppm) of the most chlorinated compound (Kanechlor 500), 30.8% developed nodular hyperplasia. Thirty percent and 31.3% of the rats developed nodular

hyperplasia when fed 1000 ppm of Kanechlor 400 and 500 ppm of Kanechlor 500 respectively. Lower doses and less chlorinated PCBs showed virtually no effect. Noteworthy is the Panel's failure to state that no hepatocellular carcinomas were found in any of the rats including those fed the highest dose-chlorination combination.

In describing (p. 20) the results from Kimbrough et al. (1975), the Panel appropriately acknowledges the substantially increased incidence of hepatocellular carcinomas and neoplastic nodules in experimental animals in this study. They go on to mention that uterine cancers were "also elevated, but not to a statistically significant level". Examination of Table 4 in the Panel's report, which presents Kimbrough's data suggests a more complex picture than the Panel's description. It can be seen that for a number of tumors incidence appears to be reduced, perhaps significantly, in the exposed animals compared to the control animals. In fact, for all tumors other than those of the liver, the incidence was somewhat greater among the control animals than in the animals fed PCBs. PCBs were also not life-shortening as almost twice as many control animals died before the experiment was terminated.

In the study of Norback and Weltman (1985), some significant findings described by the authors are not noted by the Panel. Although the striking sex-related difference in tumor rates is mentioned, the Panel did not mention that the mortality rate was not increased in the PCB exposed group.

An example of a major animal study that is not cited by the authors is that

by Schaeffer and his colleagues published in 1984. This study reported a significantly increased incidence of neoplastic nodules and hepatocellular carcinomas in Wistar rats receiving Clophen A60 (but not Clophen A30). As noted in a subsequent letter by Young (1985), this study also showed a significantly reduced risk of other tumor types and reduced mortality in both sets of PCB treated animals. Schaeffer et al. considered the protection from neoplasms of the thymus and from nephritis to be the result of PCB-induced alterations in the immune system. It is not clear why the Panel did not include this study; such an omission reduces the confidence in the completeness and balance of the review.

Another study not acknowledged by the Panel was by Kerklivet and Kimeldorf (1977) in which they reported that PCB exposure in rats, "had a significant protective effect on the host in response to the implantation and growth of Walker 256 tumor cells."

The one study of dogs was essentially negative as neither hepatocellular carcinoma nor neoplastic nodules were found in the dogs fed up to 100 ppm of Aroclor 1242, 1254 or 1260.

Five animal studies were reviewed that deal with the cancer-promoting effects of PCBs. As with the studies on carcinogenesis, the effect appears to be limited to the highest dose-chlorinated PCB compounds.

Summary of Experimental Animal Studies

1. The review of the animal studies provided by the Panel is not complete and does not include a balanced perspective on the studies.

2. In addition to the incomplete presentation of the major findings, the authors also do not provide adequate descriptions or critiques of the conduct of the studies - information that pertains to the overall interpretation and validity of the studies. For example, they do not consistently indicate overall mortality or loss of body weight. Thus it is much more difficult for the reader to evaluate these findings without searching out the original literature.

3. The studies showing an increase in hepatocellular carcinoma incidence show these increases at fairly substantial doses with the most highly chlorinated compounds.

4. Studies showing an increase in liver carcinoma did not show an increase in total tumor incidence, in fact, some show a decrease in the non-liver carcinomas.

5. In two of the studies mortality among the PCB exposed animals was actually decreased.

6. The studies do not, "demonstrate reasonable consistency" as stated in the Panel's report. The studies are inconsistent, and part of this inconsistency possibly stems from comparing the carcinogenicity of the different commercial PCB mixtures. The more highly chlorinated PCB isomers are most carcinogenic, as the Panel's report states. Kimbrough (1987) goes further, stating that it is not certain that the less chlorinated fractions (pentachlorobiphenyls and less chlorinated) cause hepatocellular carcinomas in rodents. This has implications for the

possible risk of occupational exposures, since the less chlorinated commercial mixtures (e.g. Aroclor 1242, 1254 and 1016) were more commonly used than Aroclor 1260 (Kimbrough, 1987). Of course the less chlorinated commercial mixtures are not devoid of the highly chlorinated congeners, but the concentrations of these congeners are lower in the less-chlorinated mixes (e.g. see Table 2 of the Panel's report).

7. Aroclor 1254 (as opposed to Aroclor 1260) has not definitely been shown to be hepatocarcinogenic in animals. The study most frequently reviewed is that of the National Cancer Institute (1978). There were statistically non-significant increases of hepatocellular carcinomas and hematopoietic cancers in exposed rats. Therefore, the study was equivocal at best and is negative by the criteria set for the NCI bioassays. The Panel criticizes this study on the basis of an increased mortality in the exposed groups, which they state leads to a decreased number of animals at risk for cancer in the dosed groups. While this is true, an alternative argument may also be valid. The excessive mortality in the dosed groups indicates that the doses exceeded the maximum tolerated dose and that therefore the assay is invalid. The NCI guidelines require that the maximum dose of test agent used in a bioassay be one that does not alter the animal's normal longevity unless death is due to tumors (National Cancer Institute 1976). In this NCI report it states, "A Maximum Tolerated Dose (MTD) should be selected for each sex of each strain to be used in the chronic study. The MTD is defined as the highest dose of the test agent given during the chronic study that can

be predicted not to alter the animals' normal longevity from effects other than carcinogenecity."

8. Still controversial is the relationship of hyperplastic liver nodules to the development of carcinoma. The Panel recognizes that the studies suggesting that the hyperplastic nodules are precursors of malignant tumors are, "not completely definitive". Plaa (1986) cites this interpretation as one of two theories of pathologic progression of liver cancer. Safe (1984) states that these hyperplastic nodules only appear in experimental animals after long exposure to high doses.

Human Morbidity Studies

a. Yusho Disease

Kimbrough (1987) agrees with the Panel's report that the Yusho and Yucheng poisonings can mainly be ascribed to the polychlorinated dibenzofurans (PCFOs) present in the contaminated rice oil. Kimbrough also mentions a highly toxic PCB isomer (3,4,3',4' tetrachlorobiphenyl) as being present in the contaminated oil. Kimbrough notes that this isomer has not been identified in commercial mixtures used in the U.S.

The Yusho and Yucheng episodes do not seem very relevant to the possible carcinogenic properties of PCBs. Kimbrough (1987) states that there is no definitive evidence about cancer rates in the Yusho cohort. The number of cases appearing so far has been small and a sufficient latent period may not have yet elapsed. Furthermore, although PCBs have toxicologic properties qualitatively similar to

those of polychlorinated dibenzodioxins (PCDDs) and PCDFs, the responses are not identical. In particular 2,3,7,8 dibenzodioxin (TCDD here) can induce tumors at a variety of sites in rodents, while PCBs alone have only induced liver and stomach tumors (Kimbrough, 1985). Furthermore, the exact patterns of enzyme induction of TCDD are mimicked only by a few PCB congeners having specific chlorination patterns (Safe et al., 1985).

b. Skin and Other Cutaneous Tissues

Skin lesions (acneform eruptions, folliculitis and possible skin thickening) appear to be associated with high exposure to PCBs, particularly the higher chlorinated isomers.

c. Blood Chemistry

Several studies have been conducted of workers exposed to various concentrations of PCBs in which serum blood analyses were obtained. The results from these studies are summarized in Table 12 of the Panel's report. The Panel concludes "in considering the overall results, SGOT and GGTP particularly are increased with exposure to PCBs". The results from the SGOT studies given in Table 12 show that only 3 of the 10 studies had significantly positive associations and the studies of GGTP show that 8 of 10 studies had significantly positive association. The Panel concludes that, "most of the results are negative and when positive, the effect is relatively minor."

A number of studies have looked at cholesterol and triglyceride concentration in relation to PCBs. Here the Panel overinterprets the

results summarized in Table 13. They conclude that, "statistically significant increases in triglycerides and total cholesterol were associated in some studies with increased serum PCB concentrations". However, only 8 of the 20 results in Table 13 are significantly associated.

Furthermore, the Panel notes that "some studies" did not fully control for body mass and it is not clear whether the studies showing a positive association were among those that controlled for body mass. The Panel also does not make it clear that the association can probably be explained by the increased solubility of PCBs in serum with a higher lipid content as suggested by Kimbrough (1987).

d. Liver Abnormalities

The report states that the increased serum liver enzyme levels are of uncertain clinical significance. They find more alarming a report of hepatomegaly in capacitor workers (Maroni et al, 1981), but state that this is an isolated finding. They point out (p.28) that, "Other clinical studies have not reported liver disease of such severity, if at all." It is also important to note that the study of Maroni et al. did not have a control group, nor were the examining physicians blind to the PCB exposure status of the workers. They did, however, find an association between serum PCB levels and the frequency of "abnormal" liver findings as "deduced from symptoms, clinical examination of the liver and laboratory tests."

e. Cardiovascular Effects

Generally, the associations between PCB exposure and blood pressure have disappeared when the confounding factors of age, sex, smoking and body mass were considered in the analysis. One study (Kreiss et al, 1981) did find an association with blood pressure after contolling for age, sex and body mass. Apparently smoking was not controlled and given the low PCB serum levels (average = 17.2 ppb, range 3.2 - 158), it is unlikely that the association was real.

f. Respiratory Effects

The Panel properly concludes that, "the single study indicating decreased forced vital capacity among PCB exposed workers must be confirmed in other populations".

g. Reproductive Effects

The finding from the studies on reproductive outcomes are weak and unimpressive. The Panel refers to the results as "uncertain" and "suggestive".

h. Cancer Morbidity

One study of cancer among workers is reviewed. The study has not been published in a peer-reviewed journal and apparently no control group was included. However, no case of liver cancer was reported among the exposed workers.

The Panel appropriately points out (p. 31) some of the limitations of the existing morbidity data from occupational exposures and presents

some clinical/epidemiologic considerations for future studies. They mention that an appropriate group for the study of pregnancy outcomes would be difficult to obtain. Perhaps in this regard, the potential for exposure to spouses or other household contacts of PCB exposed workers should be considered (Fischbein and Wolff, 1987).

Human Mortality Studies

The mortality studies of workers presumably exposed to PCBs are used as the foundation for the recommendations by the Panel. Four epidemiologic mortality studies have been done; one (Brown) was conducted at plants in two different states and hence, the results are presented as if 5 studies have been done. Table 15 provides the characteristics of the populations from the four major studies. Particularly noteworthy from this table is the fact that all the studies were of relatively few people and given the relative rarity of liver cancer in the population, none of the studies would have sufficient statistical power unless the magnitude of the SMR was extremely large, which apparently it is not. Somewhat troubling is the manner in which the data were pooled (meta-analysis), particularly since the panel had to rely on unpublished data provided by the authors to conduct the combined analyses. Tables 16 and 17 of the report provide the observed and expected number of deaths by cause of death for males and females from the "five" studies.

The cohort described in Table 15 for the Nicholson et al. study is not the same as the one used to obtain observed numbers of deaths in Tables 16 and 17. This is a bit misleading and confusing as it suggests that the study

size was larger than it actually was. Tables 16 and 17 include deaths among study subjects not included in the Brown study. In Table 16, the number of deaths from all causes (43) is less than the number of deaths from cardiovascular disease (53). It is also somewhat surprising that the expected and observed numbers of deaths for all causes are identical for males and females (43 observed and 45.49 expected).

Individually, the results from the studies would be interpreted as showing no association between any cause of death and employment in that particular company. However, when the observed and expected number of deaths are summed over all the studies, a significant ($p = .015$) SMR is found (see Table 18) for death from cancers of the liver, biliary passages and gallbladder based on 7 observed deaths and 2.54 expected. The Panel used a one-sided statistical test when a two-sided test would have been more appropriate. Also, since 21 comparisons were made, the conventional p value of 0.05 is not appropriate because of multiple hypothesis testing.

The Panel attempts to summarize the results within the framework of the Bradford-Hill criteria for assessing the causal significance of observational data. First, with respect to strength of the association, the Panel accepts the fact that since the SMR is statistically significant, this criterion is fulfilled. However, none of the individual studies is significant and, using the meta-analysis, the result is not sufficiently strong to satisfy this criterion (particularly if a more conservative p value and 2 tailed test are used as would be appropriate in this situation). Under consistency, no mention is made of the fact that none of

the five studies reviewed show a significant association, in fact, the studies are remarkably consistent in that they all fail to demonstrate an association between PCB exposure and liver cancer. With respect to biological plausibility in reference to the supporting evidence from animal studies, the Panel concludes that such support is apparent from the studies reviewed in the document. However, although some of the animal studies do suggest an association, they are far from conclusive as summarized in the earlier sections of this report. Furthermore, no discussion is provided on extrapolating from the doses used in the animal studies to the doses experienced by the workers in the four studies. Nor is any consideration given to the type of PCB compound. This is important because only the more highly chlorinated ones showed a carcinogenic effect with animals. Also, the general issue of extrapolating to humans from animal data is not addressed in the paper. Kimbrough (1987) states, "From empirical observations, humans also appear to be less sensitive to the toxic effects of PCBs. The ability to store these chemicals in adipose tissue may be protective."

With respect to time relationships, the Panel overlooks the fact that 4 of the 7 cases had a duration of exposure of 1 year or less (see Table 22). Furthermore, only two of the cases were actually liver cancer, the others were biliary system or gallbladder cancers and of the 7 cases, 3 were not confirmed. In their analysis, the Panel combines tumors of the liver, biliary duct and gallbladder. The justification given for this grouping is the finding of "preneoplastic lesions" in the biliary tract in a rat

study. However, there are many differences among these sites in humans with respect to geographic variations in incidence and mortality rates, secular trends, sex ratios and known or suspected risk factors (Fraumeni and Kanton, 1982; Falk, 1982). Thus grouping them is not appropriate.

Absent from the document is any discussion of confounding factors. This is particularly important given the small numbers involved in arriving at the conclusion that an association exists between PCBs and liver, biliary tract and gallbladder cancers. Seven cases were observed, 2.54 expected. It is appropriate to evaluate the potential effect on this association of a confounding factor such as alcohol use or hepatitis B infection (Falk, 1982). A small difference in the prevalence of risk factors between exposed and control groups could be of importance.

Of significance is the fact that no dose-response relationship was found. This would be another issue in evaluating the causal significance of the association. As stated in the document, "as can be seen from Table 24 [should read 23], there is no significant trend with increasing estimated risk when the durations of exposure are periods of employment in the high PCB exposed jobs". The report goes on to state, "however when the deaths in the cohort of Brown are categorized according to total plant employment as other deaths are, the distribution corresponds to an increasing risk of cancer with increasing estimated risk". This is a clear overinterpretation of the results since, as noted by the Panel, the trend is not apparent and the data are not statistically significant.

Some specific comments regarding the individual mortality studies are given below.

Brown and Jones (1981) and Brown, (1986)

As of the end of February 1988, the Brown study update had not yet appeared in the published literature. The 1981 study was published and available for review.

1. The original study reports that 163 individuals died from 1940-1976, not 160 as stated in the Panel's report.

2. In addition to not observing an increased risk with greater latency, Brown and Jones also did not observe an association with duration of employment.

3. The Panel addresses the possible impact of using U.S. mortality rates, rather than local (county) rates where plants are located, in calculating expected numbers of deaths. With respect to liver and biliary tract cancers, the Panel states that local rates were higher near one plant (Massachusetts), but lower near the other plant (New York). Three out of the 4 liver cancer or biliary tract deaths occurred in the Massachusetts cohort. This cohort also accounted for two-thirds of the total person-years (1981 study). Contrary to the assertion of the Panel, these findings do suggest a possible bias. If the higher local rate of liver cancer where the Massachusetts plant is located were used to calculate the "expected" value rather than the lower U.S. rates, a higher expected number would probably be obtained, which in turn would lower the SMR for these sites.

4. The original 1981 study found no trend in liver cancer deaths with increasing latency.

5. Brown and Jones (1981) found a trend in mortality from cirrhosis of the liver with increased length of employment which they considered to be "consistent with the notion that PCBs have a toxic effect on the liver." The SMRs increased from 74 for those employed between 3 months and 5 years to 435 for those employed between 15 and 19 years. They state that alcohol consumption is a possible confounder of the association between PCB exposure and liver cancer.

Gustavasson et al. (1986)

Several important aspects of this study were not noted by the Panel.

1. There appears to be an inconsistency in the mortality data presented in Table III in the original article. Total deaths are listed as 21. Under this Total are five major categories of deaths which sum to 27.

2. Neither the study authors nor the Panel provide the person-years of observation for this study, although study power was briefly discussed by the authors.

3. The Panel notes that this study utilized Swedish national rates to obtain expected deaths and that this may have underestimated the deaths expected in this cohort. The Panel then states that use of local rates would have, "only a trivial effect on the overall results of this review". While that may be true, the effects may not be trivial

regarding the findings of this study. The effects could be quite significant if there are large differences between local and national rates for specific tumor sites.

4. The one liver cancer (actually cancer of the ampulla of Vater) reported from this cohort was not reported as such in the original study which did not have a detailed breakdown by site. The inclusion of this case is based on a personal communication from Gustavasson to the Panel.

Bertazzi et al. (1982) and Bertazzi et al. (1987)

1. According to the Panel and the investigators, the earlier study (1982) included only production workers who had been employed for at least six months between 1946 and 1970. In the updated study (1987), several major changes were made in the definition of the study cohort. First, the eligibility period was extended to 1978. Second, the minimum period of employment was reduced from six months to one week. The authors gave two reasons for this change; one week was apparently the minimum period necessary to obtain reliable data on an employee, and less than six months of employment could produce significant exposure to PCBs. Third, all company employees, not just production employees, were included in the later study. Thus any company employee with at least one week of employment between 1946 and 1978 was included in the study.

2. The study authors did not make a particularly strong case for the changes they made in defining the study cohort, i.e., the inclusion of

nonproduction employees and those with work histories as short as one week. The evidence cited for significant short-term exposures was a 1954 study of three cases of chloracne in the company among autoclave workers who had worked 4, 6 and 7 months, respectively. Although four other cases of chloracne were diagnosed in 1977 among workers impregnating capacitors with PCBs, the work duration of these workers is not noted and neither their own data nor those of other published studies are presented to support the contention that short-term workers can generally have significant exposures. The inclusion of nonproduction workers was also not well justified. In addition to several air samples of PCBs, a number of workers were assayed for PCBs on their hands and in their blood. Unfortunately, the authors do not adequately specify the locations of the environmental samples, or provide information on how the workers were selected, their occupations or work histories. It was only stated that they represent "typical" exposure conditions. Thus, it is not at all clear that nonproduction workers or very short-term workers had significant exposures to PCBs or that the exposure potential would have been constant over different time periods. The authers do not indicate the proportion of the cohort that fell into these categories.

3. A more significant impediment to interpretation of this study is that the authors did not have available to them detailed employee work histories or job descriptions, and could not classify workers according to work history.

4. The authors did not find any relationship between mortality and length of employment, latency, or year started. However, as the authors and Panel note, the small number of deaths limit any conclusions that can be drawn.

5. It is somewhat curious that the authors presented characteristics of "selected" cases of cancer deaths in Tables VI and VII for males and females, respectively. In Table VI, they actually presented all 12 male deaths, while in Table VII, they presented only 4 of the 14 female deaths.

Nicholson et al. (1987)

This is an unpublished study, however a draft of the paper was made available for review.

1. The Panel notes that this study was conducted on one of the same plants (Plant 1, New York) that was included in the Brown and Jones study. However, the investigators defined their cohorts quite differently. Brown and Jones defined their study cohort as any worker with at least 3 months of service at any time in an area with high exposure potential - as defined by the company and corroborated by the union and a NIOSH industrial hygiene survey. The Nicholson study cohort consisted of all plant workers with at least five years of service whose employment began before 1954. Furthermore, Nicholson allowed for a 10-year latency; follow-up did not occur until after 10 years from first employment. Because of the different requirements for length of

employment and time period of employment, it is not surprising that the Nicholson cohort was smaller - 769 workers. The Panel notes that over two-thirds of these workers (521/769) were not included in the Brown and Jones cohort (and it is only data for these workers that is apparently presented in Tables 16 and 17). This finding would suggest that most of the Nicholson cohort did not have the high-exposure jobs as identified by Brown and Jones. In any event, in the absence of more detailed exposure information, it is unclear whether the Nicholson cohort or the Brown and Jones cohort provides a better or adequate study group.

Use of a Meta-Analysis

The application of meta-analysis to retrospective cohort studies is relatively new. It has been more often used for experimental studies where results from a number of randomized trials have been pooled. In these situations a number of criteria had to be met before combining the data from many studies. The Panel's report does not address the appropriateness of conducting the meta-analysis in this situation. There are no formal specifications in the Panel's report for judging that the studies were sufficiently similar to allow pooling. There were sufficient differences among the studies that could invalidate a meta-analysis. The studies were done in different countries (U.S.A., Italy and Sweden) and involved different average durations of employment, different intensities of exposure and different definitions of eligibility for inclusion into the study cohort. Bertazzi et al. did not have work histories and included all plant

employees who worked one week or more, whereas Brown and Jones included only workers with likely exposure to PCBs with at least three months of work experience. Nicholson et al. included only employees with five years of service and at least ten years of followup (latency).

Inclusion of all relevant articles is important in meta-analysis. The Panel does not stete what methods were used to ensure inclusion of all studies. Studies with negative results are less likely to be published than studies with positive results (Sacks et al, 1987). Thus, it is important to provide a well defined framework to survey the research field and identify all studies which address the issue. The Panel presumes to have identified all studies, however, they do not describe a process for conducting the search.

Summary

The panel concludes (p. 49),

"In summary, while only seven deaths from liver and biliary tract cancer occurred, the criteria of Hill for an association with exposure are reasonably well met."

The Hill criteria are not met. The only criterion that has some merit is biological plausibility.

"The association is strong (SMR = 275) and achieves statistical significance."

It is questionable if significance would be attained if a more conservative p value was used (because of multiple hypotheses testing) along with a 2-tailed test. Furthermore, 3 of the 7 cases were not confirmed.

"A finding of excess cancer is present in the workforces of four of the five plants studied; the overall excess did not come from one sporadically high finding."

Of the 5 plants in which males were studied, 2 had no deaths from cancers of the liver, biliary passages and gallbladder, 2 had 1 death and 1 had 2 deaths. Of the 4 plants which included women, 3 had no deaths from these causes and 1 plant had 3 deaths. (The latter is from an unpublished study.) Of the four published studies, Brown and Jones state, "There is no relationship between increasing duration of employment in jobs involving PCB exposure and the risk of mortality due to cancer or cirrhosis of the liver". Bertazzi et al. state, "...both workers who died from cancer of the liver and biliary tract had been employed in the production area, albeit for rather short periods". They later state, "The limitations discussed did not permit a causal assocation to be either proved or dismissed." Gustavsson et al. does not even mention the one liver cancer cited in the Panel's report but do state, "A subgroup of 19 individuals with higher exposure (capacitor fillers and repairers) was analyzed separately but there was no tendency towards an increased mortality or cancer incidence in this subgroup." And finally Nicholson, the chair of the Special Panel concludes his own study with the statement, "The overall results do not indicate any association of PCB exposure with excess mortality for any cause." A final point, the excess did indeed come mainly from one sporadically high finding. Three of the 7 deaths (43%) occurred among females in one of the plants in the Brown and Jones study.

"The concordance of the animal data and the finding of liver tumors in humans exposed to dibenzofurans, structurally similar compounds, adds weight to the human evidence."

The animal data and their limitations were in this report. Regarding the dibenzofurans (PCDFs) Kimbrough (1987a) states, "The toxicity of individual isomers of the PCBs, PCDDs (dibenzodioxins) and PCDFs varies greatly. The type of effects produced by the same compound and the target organs may differ in different species and may differ for various homologs of this mixture of chemicals. Species variations in response to PCDDs and PCDFs have some similarities, but also some differences. This makes risk estimates extremely difficult."

"The exposure and time relationship of the cancer incidence are in accord with expectations."

No dose response relationship was demonstrated in any of the individual studies nor in the combined data. Four of the 7 cases were employed for one year or less.

"Finally, no other exposure or circumstance could be identified that would provide an alternative explanation for the excess."

It must be pointed out that none of the studies considered other exposures. Important confounding factors such as alcohol use, hepatitis B virus infection or use of oral contraceptives were not considered although Brown and Jones recognized the need to consider alcohol use, particularly since they found a large increase in cirrhosis of the liver.

And finally the Panel concludes,

"Considering all the data, the evidence is strong for a causal association between the excess of these cancers and exposure to PCBs."

The evidence is not strong and the association cannot be considered causal. "Strong" and "causal" are used to describe associations such as those between cigarette smoking and lung cancer or asbestos and mesothelioma where the data are consistent and persuasive. To use these words to characterize the association between liver cancer and PCB exposure is to distort and grossly exaggerate the weak and inconsistent data that are available. The animal data are suggestive, however, the human data are weak and unconvincing.

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