UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Studies on the Health Effects of PCB

FROM: Irwin Baumel IB/cc Lee
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TO: Margaret J. Stasikowski
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As per your request, HERD staff have reviewed the documents on the various health effects of PCB toxicity. Our review is based on the six review documents and the Summary of the Health Effects of PCB (summary of the findings reported in the above six review documents) submitted by CMA. The original articles cited in these documents were not secured and evaluated. Thus, the validity of the conclusions as to the original experimentation and findings cannot be assessed without substantial efforts. Our comments are summarized in the attached paper. Contributors for the review are C. C. Lee, J. Springer, C. Jason, J. Toth, C. Nadolney, P. Hurley and D. Kram.

Attachment

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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. 2-3). This is not a relevant concern for a positive study.

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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 sentence: "...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^{-5}.

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 prefacture" 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 163 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.

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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.

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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 Kanemi 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 Kanemi 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 utilizing 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 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 depend 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 occurence 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

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.

"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.

Adverse Reproductive Outcome Discussion
(Health Effects of Electrical Grade PCBs)

I. General problems with document

A. It is impossible to discuss PCB related problems in isolation. Various amounts of PCDF are always found with PCB.

B. Many isomers of PCB are found in any mixture of PCBs, some of which are extremely toxic.

C. The fate of PCB in nature beside bioaccumulation is not clear. For example, photooxidation of PCB to PCDF does occur (Hutzinger 1974), but the probability of such occurrence in nature is not known.

D. Heating of PCBs as would occur with PCB use in heat exchangers results in increased conversion to PCDF. It is not clear how they address this issue and its inherent risk. How hot do capacitors and "closed" systems get in their life time. What conversion occurs?

E. Given the limits of our attempts to eliminate the remaining PCBs in the environment, its transport through the food chain, uncertain chemical transformations, and worrisome persistence in the animal world as the type of chlorination changes and the degree increases, it appears extremely unwise to change any position without much further work at the health and basic chemical level.

II. Deficiencies in consideration of reproductive effects

A. Increased estrogen effect may be seen via two different mechanisms.

1. Estrogen like activity which would add to or compete with endogenous estrogens (uterotrophic activity in rats, Gellett 1978).

2. Increased metabolism of endogenous estrogens through PCB effect on hepatic MFO system. These types of effects could easily account for menstrual irregularities seen as well as impair the ability to maintain the fetus.

B. Animal studies Ringer 1972, Linder 1974, Villeneuve 1971 show pronounced fertility problems depending upon PCB type and animal species at less than 50 ppm PCB.

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C. Effects on humans

1. Yusho cooking oil incident showing low birth weight/ developmental delays is of concern. Reproductive effects are seen in rhesus monkeys at 2.5-5.0 ppm by purified PCBs and in the mink, a sensitive animal species. Thus, although PCDF is admittedly dangerous PCB is not "obviously" safe.

2. Reproductive effects are being investigated in a group of women who work with capacitor grade PCBs in an Edison facility. Increased rate of low birth weight infants is one outcome under investigation by NIOSH. This type of study as well as one addressing incidence of infants with developmental delays are needed.

D. General health vs PCB

1. Given the problems of small numbers and our presently inadequate ability to address reproductive health questions of menstrual irregularities, decreased fertility, developmental delays and minimal brain dysfunction, animal studies must be given perhaps additional weight.

2. Each PCB mixture contains as many as 70 different compounds and has unique characteristics which represent a separate risk independent of its later chemical fate. Chemical transformations during use and after disposal represent yet another risk needing evaluation recognizing the uniqueness of each environmental situation.

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