Ophthalmology
The University of Michigan

February 23, 1983

William R. Gaffey, Ph.D.
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Dear Dr. Gaffey:

Enclosed is a copy of the revised manuscript which describes the mortality study of PCB workers at Monsanto. I have updated the literature review, and expanded the discussion of our results.

Judy Zack and I have discussed our ideas on the ultimate fate of this paper, as well as its strengths and weaknesses. We agree that this study has significant shortcomings - mainly due to the small numbers studied and the smaller number of deaths available for review within the cohort. Also, the reporting of SMR's in Tables 4 and 6 should include an idea of their confidence intervals or standard error, which I had no access to in revising the manuscript. Perhaps you have access to this information.

We would welcome your review of the revised manuscript and input on the merit of submitting this manuscript and, if there is merit, the appropriate journal. I will look forward to your reply.

Sincerely,

David C. Musch

David C. Musch, Ph.D.
Research Investigator

DCM:kaw

Enclosures

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A Retrospective Mortality Study of Polychlorinated Biphenyl Manufacturing Workers[1]

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Abstract

A retrospective cohort mortality study of workers exposed to polychlorinated biphenyls (PCBs) during production of the compounds is reported. A total of 89 workers exposed to PCBs for a minimum of six months during the period from 1945 to 1965 were followed through 1977, and their vital status was determined. Comparison of this PCB-exposed cohort's mortality experience with age-, race-, and cause-specific mortality rates of the U.S. male population was performed. Observed deaths were not statistically greater than expected for any of the cancer sites examined. No deaths were observed for cancer of the liver or malignant melanoma. A statistically significant excess of circulatory disease deaths, exclusive of arteriosclerotic heart disease, was observed in white males.

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The term "polychlorinated biphenyls" (PCBs) describes a group of mixed chlorinated biphenyls which vary in consistency from light, free-flowing liquids to crystalline and non-crystalline solids, depending on the degree of chlorination. PCBs have been in commercial use since 1929. Their dielectric properties, resistance to oxidation, acids, bases, and other chemicals, and thermal stability have made them useful for many applications, particularly in the production of capacitors and transformers, and in the insulation of electric cables and wires.

Reports of adverse health effects in man initiated from several incidents of accidental heavy exposure to PCBs. A process change in a chemical plant introduced an unspecified PCB compound (Arochlor) into the work environment, resulting in exposure of 14 workers to estimated breathing zone PCB levels of 0.1 mg/m^3.[1] Chloracne developed in one-half of the exposed workers, and liver function tests showed a borderline abnormality in one of the seven affected workers. After 13 months of follow-up, the chloracne had disappeared, but the liver function abnormality, although improved, remained.

Accidental ingestion of rice oil contaminated with PCBs has resulted in several outbreaks of common symptomatology, reported from Japan ("Yusho" disease)[2] and Taiwan ("Yu-Cheng" disease).[3] The most common acute symptoms observed were hyperpigmentation and acne-like lesions, discharge from the eyes, neuroendocrine disturbances, emesis, and diarrhea. There was a dose-response relationship between the amount of oil ingested and the proportion of persons reporting symptoms. After six years, many of the patients still reported such symptoms as headache, stomach pain, numbness of the extremities, arthralgia, and respiratory symptoms.[4] Although massive ingestion of PCBs occurred in these incidents, analysis of the cooking oil in the Yusho episode showed that

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polychlorinated dibenzofurans[5] and polychlorinated quaterphenyls[6] were co-contaminants. Analysis of blood samples from patients in both incidents, as well as liver and adipose tissue from Yusho patients, showed the presence of these compounds along with PCBs.[7, 8] These co-contaminants obscure the relationship of PCBs to the symptoms resulting from ingestion of the contaminated rice oils.

The Yusho incident served as a stimulus to a large number of toxicological studies dealing with the health effects of PCBs. Chronic toxicity studies of PCBs in mice and rats have shown hepatic effects ranging from hyperplasia to well-differentiated hepatocellular carcinomas following the ingestion of various PCB-containing diets.[9, 10] Studies of human exposure to PCBs have shown that body burdens are directly related to the level of exposure to PCBs.[11, 13] Morbidity studies have focused on the effects of PCBs on the skin, liver, blood chemistry, and other systems.[13, 16] Chloracne, dermatitis, mild liver function abnormalities, and increased triglycerides levels were reported with some consistency from these studies.

Mortality studies of occupationally-exposed individuals have not yielded consistent results. A preliminary report[17] addressed an increase in deaths due to malignant melanoma (2 obs. vs. 0.04 exp.), which occurred in a group of 51 research and development and 41 refinery workers at a New Jersey petrochemical plant. Another author commented on problems in defining exposures in this study.[18] In a study of 2567 capacitor plant workers exposed to PCBs,[19] excesses of liver and rectal cancer deaths, which were not statistically significant, were reported. Although few deaths were available for analysis by duration of exposure and latency, there was no trend by these measures for liver cancer deaths, and a slight increase by latency but not by length of

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exposure for rectal cancer deaths. Another study of 1310 workers from a capacitor-manufacturing plant with at least six months employment between 1946 and 1970 found statistically significant excess deaths from all cancers (in males) and all causes (in females).[20] Suggestive, but not statistically significant, excesses were noted for deaths due to digestive system cancers (in males) and malignancies of lymphatic and hematopoietic tissue (in males and females). No deaths were attributed to liver cancer or malignant melanoma. Due to the relatively young age of this worker cohort and the resultant small number of deaths (n = 27), site-specific excesses were based on two or three deaths; therefore, further study of this cohort was proposed by the authors.

At about the time of the initial report dealing with the mortality experience of an occupationally-exposed worker cohort, a preliminary review of the mortality experience of Monsanto workers involved in the production of PCBs was carried out. The present study represents a completed analysis of this worker cohort's mortality, with particular attention given to overall cancer, liver and pancreatic cancer, and malignant melanoma.

Materials and Methods

During the period from 1936 to 1977, PCBs were manufactured at Monsanto Company's Sauget, Illinois plant. Throughout this period, the process of manufacture remained relatively unchanged. This process, in brief, involved the batch chlorination of biphenyls in the presence of iron and iron chloride catalysts. The crude mixture produced in the chlorinators was then aerated, distilled, earth treated, filtered, and transferred to storage tanks before shipping. While no industrial hygiene monitoring data were available to quantify the PCB-exposure levels during the study time, interviews with plant personnel established the fact that PCB exposure levels did not vary considerably within the PCB department. Therefore, all workers in this department

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were considered to have a common exposure to PCBs, as well as other chemicals used in the department, including hydrochloric acid, tri- and tetrachlorobenzene, biphenyl, and chlorine gas.

All male employees from the hourly roll who worked in the PCB department for at least six months between January 1, 1945 and December 31, 1965 were selected for the study. By use of the plant's computerized work history system, union records, and manual work history verification, 89 male, hourly employees met the criteria for inclusion in the study. The vital status of 98.9% (88) of the cohort was determined as of December 31, 1977, using standard follow-up techniques. Table 1 summarizes the results of the vital status tracing. A death certificate was obtained for each person found to be deceased, and coding of the underlying cause of death was performed by an experienced nosologist, using the International Classification of Diseases, Adapted, Eighth Revision.[21]

Using a computer program developed for such an application,[22] the observed number of deaths among PCB workers was compared with those expected based on age-, race-, and cause-specific mortality rates of U.S. males. To compute expected numbers, person-years of observation were allocated to five-year age and calendar time categories and multiplied by corresponding race- and cause-specific death rates for U.S. males. The resulting quantities were summed over all ages and years to obtain the total expected numbers. Ratios of observed to expected number of deaths were expressed as standardized mortality ratios (SMRs). Significance testing of the SMRs was performed at the 5% level, assuming that the observed number of deaths follow a Poisson distribution.[23]

Results

Of the 88 PCB workers for whom vital status tracing was successful, 58 were verified living and 30 were verified deceased. Death certificates were

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obtained for each of the decedents. The person-years of observation contributed by the entire worker cohort are shown in Table 2. A total of 1800.1 person-years were observed at all ages, with the majority observed in the middle-age range (ages 35-60 yrs. contributed 74%, or 1333.1 person-years to the total). Cross-classification of PCB exposure duration with vital status (Table 3) shows that the majority of both living and deceased workers were exposed less than three years. The average length of exposure to PCBs for living and deceased workers was similar, with deceased workers having slightly more exposure time (3.7 yrs. vs. 3.2 yrs., respectively).

Cause-specific SMRs are listed in Tables 4 and 5 for the 60 white and 29 nonwhite male members of the PCB study cohort. Deaths due to malignant neoplasms, as indicated in Table 4, accounted for 27% (8) of the total number of deaths. No cancer deaths were attributed to malignant neoplasms of the liver or pancreas, or malignant melanoma. While many of the cancer-specific SMRs exceed 100, none are statistically significant. In white males, lung cancer accounted for 75% of the deaths due to malignant neoplasms, while no single cause predominates in nonwhite males. Table 5 presents a brief summary of the eight cancer deaths in the PCB worker cohort.

Among the non-malignant causes of death (Table 6), diseases of the circulatory system accounted for almost half of the deaths. For the category of circulatory system disease, exclusive of arteriosclerotic heart disease, the SMRs for white males and for the total cohort were significantly greater than 100. The excess in deaths due to this category is accounted for solely by the experience of the white males, since nonwhite males showed an SMR of 93. No other causes of death in Table 6 showed observed deaths which were statistically

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greater than expected. The overall SMR for malignant and non-malignant causes was 131 (30 observed, 22.88 expected deaths). Little difference was found in this overall SMR by race (for whites, 133; for nonwhites, 128).

Discussion

This investigation dealt with the mortality experience of a cohort of 89 male workers involved for a least six months in the production of PCBs between January 1, 1945 and December 31, 1965. The only cause of mortality which showed a statistically significant excess in observed deaths was circulatory diseases exclusive of arteriosclerotic heart disease. This excess was apparent only for white males. Circulatory diseases in this category included deaths from rheumatic heart disease, cerebrovascular disease, and other forms of heart disease.

If this excess cause of death is not an artifact, one would postulate that there may also be a relation between risk factors of these circulatory diseases and PCB exposure. Blood pressure, a risk factor (when elevated) of coronary heart disease (CHD) and cerebrovascular disease, has been related to blood PCB levels in two studies, with conflicting results. One study[24] found that serum PCB levels made a statistically significant contribution to explaining the variability of diastolic (but not systolic) blood pressure measurements in multiple regression analyses of data from a community exposed to DDT and PCBs, while another study[25] found no such association. Studies of lipids, which have been associated with CHD and (with less consistency) with cerebrovascular disease, have considered total cholesterol, high density lipoprotein (HDL), and triglyceride levels in relation to blood PCB levels. While no consistent association has been shown between blood PCBs and total cholesterol or HDL levels, most,[13, 16] but not all,[24] studies have shown increased triglyceride

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levels with increased blood PCB levels. Given the lack of support for an association between PCBs exposure and non-ASHD circulatory system deaths from previously reported mortality studies, and the inconclusive relation between cardiovascular risk factors and blood PCBs, this excess cause of death must be viewed as a preliminary finding, in need of support from other studies.

While previous mortality studies as well as toxicological studies have implicated a variety of cancers - digestive system, liver, pancreas, malignant melanoma - as possible results of exposure to PCBs, the present study provides no support to such findings. In the Monsanto worker cohort, no deaths were attributed to liver or pancreatic cancer, nor were any malignant melanomas found. The overall excess in cancer deaths, while not statistically significant (8 observed, 4.46 expected, SMR = 179), is mainly a result of respiratory cancer deaths in workers for whom smoking habits were not ascertained.

Although the present study's results do not support a carcinogenic effect associated with PCB exposure, there are significant limitations to the results. A principal limitation is the size of the worker cohort, which prevents the detection of increases in risk to deaths from rare diseases. A much larger cohort followed for a longer period would be necessary to detect a two-fold increase, for example, in observed liver cancer deaths. In order to allow for a latency period, the study cohort was limited to those working at least six months until December, 1965. Since PCB production continued until 1977, further follow-up of the mortality of Monsanto's PCB-exposed workers will have larger numbers, as well as longer follow-up time.

Another limitation common to retrospective studies of occupational cohorts is lack of knowledge of exposures from other work-related activities. While personal habits, such as smoking and drinking, can sometimes be roughly ascertained if co-workers or family members are available for interview, previous

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exposures, or concurrent occupational exposures during follow-up, are often impossible to assess. The connection of an effect to a previous PCB exposure must first consider other potential effect-related exposures.

A useful comparison group in occupational mortality studies is an unexposed industrial cohort, from the same plant, if possible. Ascertainment of mortality of such a cohort allows for comparison of SMRs between exposed and unexposed cohorts, which reduces the possibility that an elevated cause of death in the exposed cohort is a result of a generally greater than expected cause-specific mortality in that area or industry. Such a comparison group would have been useful in evaluating the elevated mortality due to non-ASHD circulatory system diseases found in this study.

Given the size of the study cohort and the other limitations described above, the results of this analysis of PCB-exposed workers' mortality experience are not definitive, but rather contribute to the health-effects research on PCBs. A future study of this cohort could evaluate the mortality of workers involved from the initial through the final year of PCB production, and thus have more power to detect any possible hazards of PCB exposure.

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Table 1

Follow-up Status of Polychlorinated Biphenyl Workers as of December 31, 1977

Follow-up Status	Number
Status known	88
Verified alive	58
Verified deceased	30
Death certificate found	30
Death certificate not found	0
Status Unknown	1
Total	89

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Table 2

Person-years of Observation Contributed by Polychlorinated Biphenyl Workers by Age

Age in Years	Person-years of Observation
20-24	11.4
25-29	63.8
30-34	142.6
35-39	222.5
40-44	283.2
45-49	325.3
50-54	294.5
55-59	207.6
60-64	134.0
65+	115.2
Total	1800.1

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Table 3

Duration of Exposure to Polychlorinated Biphenyls by Vital Status

Years of Exposure*	Vital Status: Living (n = 58)	Deceased (N = 30)	Unknown (n = 1)	Total (n = 89)
<1	20	5	1	26
1-3	20	12	0	32
3-5	6	4	0	10
>5	12	9	0	21
Average Length of Exposure	3.2 yrs.	3.7 yrs.	0.7 yrs.	3.3 yrs.

*Lifetime exposure prior to 1-1-66

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Table 4

Observed and Expected Deaths Due to Malignant Neoplasms by Race, PCB Worker Cohort

I.C.D. No. (Eighth Rev.)	Cause of Death	White Males				Nonwhite Males				Total			
		O	E	SMR*	SE	O	E	SMR*	SE	O	E	SMR*	SE
140-209	All Malignant neoplasms	4	2.70	148	74	4	1.76	227	114	8	4.46	179	63
140-149	Buccal cavity & pharynx	0	0.09	-		0	0.07	-		0	0.16	-	
150-159	Digestive organs & peritoneum	0	0.75	-		1	0.58	172	172	1	1.33	75	75
155, 156	Liver	0	0.05	-		0	0.05	-		0	0.10	-	
150-154, 157-159	Other digestive organs	0	0.70	-		1	0.53	189	189	1	1.23	81	81
160-163	Respiratory system	3	0.94	319	184	1	0.59	169	169	4	1.53	261	131
162, 163	Lung	3	0.89	337	195	1	0.55	182	182	4	1.44	278	139
160, 161	Other respiratory organs	0	0.05	-		0	0.04	-		0	0.09	-	
185-189	Genitourinary organs	0	0.28	-		1	0.23	435	435	1	0.51	196	196
200-209	Lymphatic & hematopoietic tissue	0	0.28	-		1	0.12	833	833	1	0.40	250	250
164-184, 190-199	All other sites	1	0.36	278	278	0	0.17	-		1	0.53	189	189

*No SMR was statistically significant (all p-values greater than 0.05)

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Table 5

Case Summaries of Cancer Deaths Among Polychlorinated Biphenyl Workers

Race	Year of Birth	Year of First Exposure	Year of Death	PCB Exposure Duration (mo.)	Death Certificate Cause of Death (ICD#)
Nonwhite	1909	1942	1959	13	Carcinoma of colon (153.8)
Nonwhite	1913	1954	1965	85	Carcinomatosis-Primary site, kidney (189.0)
Nonwhite	1909	1951	1968	28	Carcinoma of lung (162.1)
White	1893	1943	1963	34	Carcinoma of right lung (162.1)
White	1912	1951	1968	28	Carcinoma of lung (162.1)
White	1916	1951	1977	33	Carcinoma of lung (162.1)
Nonwhite	1907	1945	1964	8	Multiple myeloma (203.0)
White	1906	1940	1957	79	Metastatic carcinoma-carcinomatosis (199.0)

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Table 6

Observed and Expected Deaths Due to Non-malignant Causes by Race, PCB Worker Cohort

I.C.D. No. (Eighth Rev.)	Cause of Death	White Males				Nonwhite Males				Total			
		O	E	SMR	SE	O	E	SMR	SE	O	E	SMR	SE
390-458	Diseases of the circulatory system	11	6.82	161	49	5	4.35	115	51	16	11.17	143	36
410-413	Arteriosclerotic heart disease	4	4.99	80	40	3	2.20	136	79	7	7.19	97	37
390-409, 414-458	All other circulatory system	7	1.83	526*	145	2	2.15	93	66	9	3.98	226*	75
460-519	Diseases of the respiratory system	0	0.73	-		1	0.54	185	185	1	1.27	79	79
520-577	Diseases of the digestive system	1	0.75	133	133	1	0.45	222	222	2	1.20	167	118
800-998	External causes of death	0	1.43	-		1	0.95	105	105	1	2.38	42	42
-	All other non-malignant causes	2	1.10	182	129	0	1.30	-		2	2.40	83	59
Total	All causes, malignant & non-malignant	18	13.53	133	31	12	9.35	128	37	30	22.88	131	24

*$p < 0.05$

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