

Monsanto

DEPARTMENT OF MEDICINE &
ENVIRONMENTAL HEALTH

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September 15, 1982

Mr. David P. Brown
Assistant Chief
Industrywide Studies Branch
NIOSH
4676 Columbia Parkway
Cincinnati, Ohio 45226

Dear Dave:

Enclosed is the Zack and Musch paper that we discussed over the telephone. Any final draft of this will differ in the background section but not in the numbers in the tables. Since EPA has this draft and since it was referred to in EPA's mini-symposium I see no problem in summarizing the results for Dr. Wade, but I would prefer that you not send him a copy just in case a slightly different version gets published.

Yours sincerely,

Bill Gaffey

William R. Gaffey, Ph.D.
Manager, Epidemiology

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Enclosure

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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 stuay 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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References

1. Meigs, J.W., Albom, J.J., Kartin, B.L. Chloracne from an unusual exposure to Arochlor. J.A.M.A. 154:1417-1418, 1954.
2. Kuratsune, M., Yoshimura, T., Matsuzaka, J., Yamaguchi, A. Epidemiology study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. Environ. Health Persp. 1:119-128, 1972.
3. Chang, K.J., Cheng, J.S. Huang, P.C., Tung, T.C. Study of patients with PCB poisoning. J. Formosan Med. Assoc. 79:304-313, 1980.
4. Urabe, H., Koda, H., Asahi, M. Present state of Yusho patients. Ann. N.Y. Acad. Sci. 320:273-276, 1979.
5. Nagayama, J., Kuratsune, M., Masuda, Y. Determination of chlorinated dibenzofurans in Kanechlors and "Yusho oil." Bull. Environ. Contam. Toxicol. 15:9-13, 1976.
6. Kamps, L.R., Trotter, W.J., Young, S.J., Carson, L.J., Roach, J.A.G., Sphon, J.A., Tanner, J.T., McMahon, B. Polychlorinated quaterphenyls identified in rice oil associated with Japanese "Yusho" poisoning. Bull. Environ. Contam. Toxicol. 20:589-591, 1978.
7. Kashimoto, T., Miyata, H., Kunita, N. The presence of polychlorinated quaterphenyls in the tissues of Yusho victims. Food Cosmetics Toxicol. 19:335-340, 1981.
8. Kashimoto, T., Miyata, H., Kunita, S., Tung, T.C., Hsu, S.T., Chang, K.J., Tang, S.Y., Ohi, G., Nakagawa, J., Yamamoto, S. Role of polychlorinated dibenzofuran in Yusho (PCB poisoning). Arch. Environ. Health 36:321-326, 1981.

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9. Kimbrough, R.D., Linder, R.E., Gaines, T.B. Morphological changes in livers of rats fed polychlorinated biphenyls. Arch. Environ. Health 25:354-364, 1972.

10. Kimbrough, R.D., Squire, R.A., Linder, R.E., Strandberg, J.D., Montali, R.J., Burse, V.W. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Arochlor 1260. J. National Cancer Inst. 55:1453-1459, 1975.

11. Ouw, H.K., Simpson, G.R., Siyali, D.S. Use and health effects of Arochlor 1242, a polychlorinated biphenyl, in an electrical industry. Arch. Environ. Health 31:189-194, 1976.

12. Maroni, M., Colombi, A., Cantoni, S., Ferioli, E., Foa, V. Occupational exposure to polychlorinated biphenyls in electrical workers. I. Environmental and blood polychlorinated biphenyls concentrations. Brit. J. Industr. Med. 38:49-54, 1981.

13. Chase, K.H., Wong, O., Thomas, D., Berney, B.W., Simon, R.K. Clinical and metabolic abnormalities associated with occupational exposure to polychlorinated biphenyls (PCBs). J. Occup. Med. 24:109-114, 1982.

14. Fischbein, A., Wolff, M.S., Lilis, R., Thornton, J., Selikoff, I.J. Clinical findings among PCB-exposed capacitor manufacturing workers. Ann. N.Y. Acad. Sci. 320:703-715, 1979.

15. Marcni, M., Colombi, A., Arbosti, G., Cantoni, S., Foa, V. Occupational exposure to polychlorinated biphenyls in electrical workers. II. Health effects. Brit. J. Industr. Med. 38:55-60, 1981.

16. Baker, E.L., Jr., Landrigan, P.J., Glueck, C.L., Zack, M.M., Jr., Liddle, J.A., Burse, V.W., Houseworth, W.J., Needham, L.L. Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am. J. Epidemiol. 112:553-563, 1980.

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17. Bahn, A.K., Rosenwaike, I., Herrmann, N., Grover, P., Stellman, J., O'Leary, K. Melanoma after exposure to PCBs. N. Engl. J. Med. 295:450, 1976.

18. Lawrence, C. PCB? and melanoma. N. Engl. J. Med. 296:108, 1977.

19. Brown, D.P., Jones, M. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch. Environ. Health 36:120-129, 1981.

20. Bertazzi, P.A., Zocchetti, C., Guercilena, S., Foglia, M.D., Pesatori, A., Riboldi, L. Mortality study of male and female workers exposed to PCBs. Int. Symposium on Prev. of Occup. Cancer, Helsinki, Finland, April, 1981.

21. Eighth Revision, International Classification of Diseases, Adapted for Use in the United States. U.S. Department of Health, Education, and Welfare, Public Health Service, PHS Publication No. 1693. Washington: U.S. Government Printing Office, 1977.

22. Monson, R.R. Analysis of relative survival and proportional mortality. Comput. Biomed. Res. 7:325-332, 1974.

23. Bailar, J.C., Ederer, F. Significance factors for the ratio of a Poisson variable to its expectation. Biometrics 20:639-643, 1964.

24. Kreiss, K., Zack, M.M., Kimbrough, R.D., Needham, L.L., Smrek, A.L., Jones, B.T. Association of blood pressure and polychlorinated biphenyl levels. J.A.M.A. 245:2505-2509, 1981.

25. Bumgarner, J.E., Hammer, D.I., Colucci, A.V., Creason, J.P., Finklea, J.F. Polychlorinated biphenyl residues in refuse workers. Research Triangle Park, North Carolina, National Institute of Environmental Health and Safety, Public Health Service, Department of Health, Education, and Welfare, 10 pp., 1973.

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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*	O	E	SMR*	O	E	SMR*
140-209	All Malignant neoplasms	4	2.70	148	4	1.76	227	8	4.46	179
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	1	1.33	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	1	1.23	81
160-163	Respiratory system	3	0.94	319	1	0.59	169	4	1.53	261
162, 163	Lung	3	0.89	337	1	0.55	182	4	1.44	278
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	1	0.51	196
200-209	Lymphatic & hematopoietic tissue	0	0.28	-	1	0.12	833	1	0.40	250
164-184, 190-199	All other sites	1	0.36	278	0	0.17	-	1	0.53	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	O	E	SMR	O	E	SMR
390-458	Diseases of the circulatory system	11	6.82	161	5	4.35	115	16	11.17	143
410-413	Arteriosclerotic heart disease	4	4.99	80	3	2.20	136	7	7.19	97
390-409, 414-458	All other circulatory system	7	1.83	526*	2	2.15	93	9	3.98	226*
460-519	Diseases of the respiratory system	0	0.73	-	1	0.54	185	1	1.27	79
520-577	Diseases of the digestive system	1	0.75	133	1	0.45	222	2	1.20	167
800-998	External causes of death	0	1.43	-	1	0.95	105	1	2.38	42
-	All other non-malignant causes	2	1.10	182	0	1.30	-	2	2.40	83
Total	All causes, malignant & non-malignant	18	13.53	133	12	9.35	128	30	22.88	131

*$p < 0.05$

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February 27, 1985

David P. Brown
National Institute for Occupational
Safety and Health
Robert A. Taft Laboratories
4676 Columbia Parkway
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MAR 4 1985

Dear David:

Enclosed is a photocopy of the report "Mortality of PCB Workers at the Monsanto Plant in Sauget, Illinois" by Judith Zack and David Musch. As far as I know, this is the final report, although the report was never published in the scientific literature.

It was good hearing from you yesterday. I will be attending the NIOSH Dioxin Registry meeting in Cincinnati on March 14-15, 1985, and I am looking forward to seeing the old crew that is still working at NIOSH.

Sincerely,

Terry L. Leet

Terry L. Leet

Enclosure

cc: W.R. Gaffey

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Mortality of PCB Workers at the Monsanto Plant in Sauget, Illinois

Judith A. Zack and David C. Musch
December 14, 1979

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Summary

An historical prospective mortality study was conducted on workers exposed to polychlorinated biphenyls at the Monsanto Company plant in Sauget, Illinois. Eighty-nine workers exposed to PCBs for a minimum of six months during the period 1945 to 1965 were followed for their mortality experience. Observed deaths were not statistically different from expected deaths for any of the cancer sites examined. No deaths were observed from cancer of the liver or pancreas or from malignant melanoma. No excess was seen in deaths from liver cancer. A statistically significant excess of circulatory disease, exclusive of arteriosclerotic heart disease, was seen in white males.

Background

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 commerical use since 1929. Their electrical properties, fire resistance, and inertness have made them popular for many applications. They have been used particularly in the production of electric capacitors and transformers and in the insulation of electric cables and wires.

Reports of adverse health effects in man and carcinogenic effects in certain animals species prompted the National Institute of Occupational Safety and Health (NIOSH) to request that epidemiological studies be carried out on PCB-exposed worker populations. In a preliminary study of workers exposed to PCBs at the Mobil Oil Company plant in Paulsboro, New Jersey, Bahn reported an excess of deaths from malignant melanoma and pancreatic cancer among research and production employees.[1] At the same time, Roush reported the findings of a preliminary mortality study of PCB workers at the Monsanto Company plant in Sauget, Illinois (G. Roush, written communication, September 1976). No cases of malignant melanoma or pancreatic cancer were found.

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The accidental poisonings with PCBs in Yusho, Japan provide information on the acute toxic effects of PCBs for man. PCB poisoning occurred following the ingestion of Kanemi rice oil contaminated with PCBs. The general symptoms of Yusho disease included neuroendocrine disturbances, abnormal lipid metabolism, disturbances of the respiratory system, acneform eruption, pigmentation, and ocular changes.[2] Yusho disease, however, has also been attributed to the ingestion of polychlorinated dibenzofurans (PCDFs) present in the rice oil as PCB contaminant. The presence of PCDFs obscurs the relationship of PCBs to the clinical picture of Yusho disease.

In 1976, the Monroe County Board of Health conducted biochemical tests among Bloomington, Indiana residents exposed to PCBs. Serum levels of gamma glutamyl transpeptidaise and plasma triglyceride levels were found to show a direct relationship to serum PCB levels.[3]

In a recent study, Warshaw et al. evaluated pulmonary function in 243 workers exposed to PCBs in the manufacture of capacitors.[4] Thirty-four of these workers (14%) were found to have abnormal forced vital capacity measurement. Of these thirty-four, twenty-seven demonstrated a restricted pattern of impairment with virtually no radiographic change The relationship between restrictive spirometric impairment and duration of PCB exposure was not addressed in this study.

Extensive studies of PCB toxicity for animals have been conducted and have been throughly reviewed.[5] In a two-year chronic oral toxicity test of PCBs, no carcinogenic effects were observed in the rats and beagles tested. Hyperplasia, hypertrophy, extensive fibrosis, and several benign tumors were observed in the livers of the rats, but there was no evidence of malignancy of any of the test animals.[6]

Other investigators have reported liver tissue effects ranging from hyperplasia to well-differentiated hepatocellular carcinomas in rats or mice fed with various PCB-containing diets. Kimbrough fed rats PCBs and observed lipid accumulation, hypertrophy, and adenofibromas, but no maligancies in the livers of the test animals.[7] In a later

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experiment, the same researcher reported the induction of hepatocellular carcinomas and neoplastic nodules of the liver.[8]

The literature on PCB toxicity points to several organ sites in man that could potentially incur toxic effects of exposure to PCBs. The present study represents a completed analysis of the preliminary study of Monsanto PCB workers reported in 1976. This study will examine the mortality experience of PCB workers with particular attention given to overall cancer, liver and pancreatic cancer, and malignant melanoma.

Population and Methods

This study focused on workers exposed to polychlorinated biphenyls at the Monsanto plant in Sauget, Illinois. PCBs were manufactured at this plant during the period 1936 to 1977. 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 study.

During the period of study, the PCB process remained relatively unchanged The 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 aerated, distilled, earth treated, filtered and transferred to storage tanks. No industrial hygiene data were available to quantify the PCB exposure levels. Through interviews with plant personnel, it was determined that exposure levels to PCB did not vary considerably within the PCB department. Therefore, all workers in the PCB department were considered to have common exposure level. Other exposures in this department included hydrochloric acid, tri- and tetrachlorobenzene, biphenyl, and chlorine gas.

The PCB worker cohort was identified from the plant's computerized work history system. Eighty-nine male hourly employees met the criteria for inclusion in the study. The vital status of each member was determined as of December 31, 1977, using standard followup techniques. A death certificate was obtained for each person found to be deceased.

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The underlying cause of death was coded to the Eighth Revision of the International Classification of Disease, Adapted[8] by an experienced independent nosologist.

The data were analyzed by the modified life table method using the Monson program.[9] Standardized mortality ratios were calculated for nineteen selected cause-of-death categories. Mortality comparisons were made with the general U.S. population. Statistical significance was determined at the 5% level assuming a Poisson distribution.

Results

Eighty-eight of the eighty-nine members of the study cohort were traced. Fifty-eight were verified living and thirty were verified deceased by death certificate. The results of this vital status tracing are shown in Table 1.

The person-years of observation contributed by the eighty-nine member study cohort are shown in Table 2. A total of 1800.1 person-years were observed at all ages. Most of these person-years were observed in the middle-age range with 1333.1 person-years (74%) observed for ages 35-60.

Table 3 categorizes duration of exposure to PCBs by vital status. For both living and deceased workers, the majority were exposed less than three years. The next frequent exposure class was for five or more years of exposure. The least number of workers fell in the three to five years of exposure category. Overall, the average length of exposure for living and deceased workers was similar with deceased workers having 3.7 years of exposure and living workers having slightly less at 3.2 years.

The mortality experience for all males is summarized in Table 4. The mortality of white and nonwhite males is examined separately in Tables 5 and 6. Observed and expected deaths and SMR's are shown for each of the nineteen cause-of-death categories examined.

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For all males, there were 30 deaths observed and 22.88 expected (Table 4) The overall SMR was 131. For malignant neoplasms, 8 deaths were observed with 4.46 expected. The SMR for all malignant neoplasm was 179. No deaths were observed from liver or pancreatic cancer or from malignant melanoma. The SMR for lung cancer was high at 278. The only statistically significant difference seen in this table is seen for diseases of the circulatory system, exclusive of arteriosclerotic heart disease. Nine deaths were observed with 3.98 expected, yielding a SMR of 226.

Table 5 shows the overall SMR remains high for white males at 133. There were 4 deaths from cancer with 2.70 expected. None were from liver or pancreatic cancer or from malignant melanoma. The high SMR's seen in Table 4 for lung cancer and the residual diseases of the circulatory system appear to be explained by the high SMR's for these causes in white males. There were 3 deaths observed from lung cancer with 0.94 expected, yielding a SMR of 319. For the category of circulatory disease, exclusive of arteriosclerotic heart disease, the SMR was 526 with 7 observed and 1.83 expected deaths. This difference was the only one of statistical significance in this table.

For nonwhite males, there were no statistically significant differences seen in Table 6. The overall SMR was also high at 128. Four deaths from cancer were observed with 1.76 expected, but none from liver or pancreatic cancer or from malignant melanoma.

Case histories for the eight cancer deaths are summarized in Table 7.

Discussion

The results of this study do not corroborate an excess risk of pancreatic cancer or malignant melonoma among workers exposed to PCBs as reported in the study of Mobil workers. Nor do the results uphold translating to man the outcome of animal tests, in which hepatomas have been associated with long-term PCB exposure. In this study, no deaths were ob-

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served from pancreatic or liver cancer or from malignant melanoma.

The SMR for all causes was elevated from what one would expect in an industrial cohort. The high SMR for white males is, for the most part, explained by the excess in deaths from circulatory diseases exclusive of arteriosclerotic heart diseases. This cause-of-death category includes deaths from rheumatic heart disease, cerebrovascular disease, and other forms of heart disease, all of which are unlikely to be related to exposure in the workplace. It is urged that a larger study to be undertaken of the total Krummrich plant population to evaluate the overall risk of death from all causes and from cardiovascular diseases.

WATER_PCB-SD0000010701

References

1. Bahn Ak, Rosenwaike I, Herrmann N, et al: Melanoma after Exposure to PCB's. NEJM 295:450, 1977

2. Kuratsune M, Masuda Y, Nagayama J: Some of the Recent Findings Concerning Yusho, in Proceedings of the National Conference on Polychlorinated Biphenyls, November 19-21, 1975, Chicago, EPA-560/6-75-004. US Environmental Protection Agency, Office of Toxic Substances, 1976, pp 14-29

3. Morbidity and Mortality Weekly Report: Polychlorinated Biphenyl Exposure - Indiana. Center for Disease Control, 27 (12):99-100, 1978

4. Warshaw R, Fischbein A, Thorton J, et al: Decrease in Vital Capacity in PCB-exposed Workers in a capacitor manufacturing facility. In Health Effects of Halogenated Aromatic Hydrocarbons, Annals of the New York Academy of Sciences, New York, 1979. Vol 320

5. International Agency for Research on Cancer: Polychlorinated biphenyls and Polybrominated biphenyls. Iarc Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Lyon, 18, October 1978

6. Kimbrough RD, Linder RE, Gaines TB: Morphological changes in liver of rats fed with polychlorinated biphenyls. Arch Environ Health 25:354-364, 1972

7. Kimbrough RD, Squire RA, Linder RE, et al: Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. J. National Cancer Inst. 55:1453-1459, 1975

8. Eighth Revision, International Classification of Diseases, Adapted for Use in the United States. U.S. Department of Health, Education and Welfare, Public Health Service, PHS Publication No. 1693. Washington: U.S. Government Printing Office, 1977

9. Monson RR: Analysis of relative survival and proportional mortality. Comput Biomed Res 7:325-332, 1974

WATER_PCB-SD0000010702

Table 1

Polychlorinated Biphenyl Workers -
Results of Tracing as of 12/31/77

Total to be traced	89
Status Known	88
Verified Alive	58
Verified Dead	30
Death Certificate Found	30
Death Certificate Not Found	0
Status Unknown	1

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Table 2

Person-Years of Observation Contributed by Workers
Exposed to PCB's by Five Year Age Groups

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 - All Workers	1800.1

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Table 3

Duration of Exposure to PCB's for Workers by Vital Status

Years of Exposure	Living N=58	Deceased N=30	Unknown N=1	Total N=89
< 1 yr.	20	5	1	26
1-3 yrs.	20	12	0	32
3-5 yrs.	6	4	0	10
> 5 yrs.	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, All Males

I.C.D. No. (Eighth Rev.)	Cause of Death	Observed	Expected	SMR
	All causes of death	30	22.88	131
140-209	All malignant neoplasms	8	4.46	179
140-149	Buccal cavity and pharynx	0	0.16	-
150-159	Digestive organs and peritoneum	1	1.33	75
155,156	Liver	0	0.10	-
-	All other digestive organs	1	1.23	81
160-163	Respiratory system	4	1.53	261
162,163	Lung	4	1.44	278
-	All other respiratory organs	0	0.09	-
185-189	Genitourinary organs	1	0.51	196
200-209	Lympatic and hematopoietic tissue	1	0.40	250
-	Other sites	1	0.53	189
390-458	Diseases of the circulatory system	16	11.17	143
410-413	Arteriosclerotic heart disease	7	7.19	97
-	All other diseases of the circulatory system	9	3.98	226*
460-519	Diseases of the respiratory system	1	1.27	79
520-577	Diseases of the digestive system	2	1.20	167
-	All other diseases	2	2.40	83
800-998	External causes of death	1	2.38	42

Number of persons observed = 89

* $p < .05$

WATER_PCB-SD0000010706

Table 5

Observed and Expected Deaths, White Males

I.C.D. No. (Eighth Rev.)	Cause of Death	Observed	Expected	SMR
	All causes of death	18	13.53	133
140-209	All malignant neoplasms	4	2.70	148
140-149	Buccal cavity and pharynx	0	0.09	-
150-159	Digestive organs and peritoneum	0	0.75	-
155,156	Liver	0	0.05	-
-	All other digestive organs	0	0.70	-
160-163	Respiratory system	3	0.94	319
162,163	Lung	3	0.89	337
-	All other respiratory organs	0	0.05	-
185-189	Genitourinary organs	0	0.28	-
200-209	Lymphatic and hematopoietic tissue	0	0.28	-
-	Other sites	1	0.36	278
390-458	Diseases of the circulatory system	11	6.82	161
410-413	Arteriosclerotic heart disease	4	4.99	80
-	All other diseases of the circulatory system	7	1.83	526*
460-519	Diseases of the respiratory system	0	0.73	-
520-577	Diseases of the digestive system	1	0.75	133
-	All other diseases	2	1.10	182
800-998	External causes of death	0	1.43	-

Number of persons observed = 60

*$p < .05$

WATER_PCB-SD0000010707

Table 6

Observed and Expected Deaths, Nonwhite Males

I.C.D. No. (Eighth Rev.)	Cause of Death	Observed	Expected	SMR
	All causes of death	12	9.35	128
140-209	All malignant neoplasms	4	1.76	227
140-149	Buccal cavity and pharynx	0	0.07	-
150-159	Digestive organs and peritoneum	1	0.58	172
155,156	Liver	0	0.05	-
-	All other digestive organs	1	0.53	189
160-163	Respiratory system	1	0.59	169
162,163	Lung	1	0.55	182
-	All other respiratory organs	0	0.04	-
185-189	Genitourinary organs	1	0.23	435
200-209	Lymphatic and hematopoietic tissue	1	0.12	833
-	Other sites	0	0.17	-
390-458	Diseases of the circulatory system	5	4.35	115
410-413	Arteriosclerotic heart disease	3	2.20	136
-	All other diseases of the circulatory system	2	2.15	93
460-519	Diseases of the respiratory system	1	0.54	185
520-577	Diseases of the digestive system	1	0.45	222
-	All other diseases	0	1.30	-
800-998	External causes of death	1	0.95	105

Number of persons observed = 29

WATER_PCB-SD0000010708

Table 7

Case Summaries of Cancer Deaths Among PCB Workers

Race	Year of Birth	Year of First Exposure	Year of Death	Duration Ever Exposed to PCB's	Death Certificate Statement of Cause of Death
Nonwhite	1909	1942	1959	1 yr., 1 mo.	Carcinoma of colon (153.8)
Nonwhite	1913	1954	1965	7 yrs., 1 mo.	Carcinomatosis - primary site kidney (189,0)
Nonwhite	1909	1951	1968	2 yrs., 4 mos.	Carcinoma of the lung (162.1)
White	1893	1943	1963	2 yrs., 10 mos.	Carcinoma right lung (162.1)
White	1912	1951	1968	2 yrs., 4 mos.	Cancer of lung (162.1)
White	1916	1951	1977	2 yrs., 9 mos.	Carcinoma of lung (162.1)
Nonwhite	1907	1945	1964	8 mos.	Multiple myeloma (203.0)
White	1906	1940	1957	6 yrs., 7 mos.	Metastatic carcinoma - carcinomatosis (199.0)

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