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MORTALITY OF WORKERS EXPOSED TO POLYCHLORINATED BIPHENYLS - AN UPDATE

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Abstract

A retrospective cohort mortality study of workers exposed to polychlorinated biphenyls (PCBs) in two plants manufacturing electrical capacitors was reported in 1981. The study was conducted primarily to examine the risk of cancer mortality associated with exposure to PCBs. Due to small numbers of deaths and a relatively short observation period, that study was considered inconclusive. This study has been updated by adding seven years of observation. The number of deaths in the study cohort has increased from 163 to 295. Mortality from all causes was found to be lower than expected (295 observed versus 318 expected deaths) as well as mortality from all cancers (62 observed versus 80 expected deaths). A statistically significant excess in deaths from cancer of the liver and biliary passages was observed (5 observed versus 1.9 expected; $p < 0.05$). Most of this excess was observed in women employed in one plant; and due to the small numbers of deaths, it remains difficult to interpret these findings in regard to PCB exposure. This cause of death is of particular interest because PCBs have been shown to cause liver tumors in laboratory animal studies.

Introduction

In 1981¹ the results from a retrospective cohort mortality study of 2567 workers employed in two plants where PCBs were used to manufacture electrical capacitors was reported. The purpose of that study was to determine whether occupational exposure to PCBs was associated with long term health effects, particularly cancer. Based on the animal data,²⁻⁶ cancer and more

specifically liver cancer were the diseases of most concern. The study population included workers with at least three months of employment in areas of the plants considered to represent the potential for the heaviest occupational exposure to PCBs. The two plants were located in Upper New York State (Plant 1) and Massachusetts (Plant 2). The results of that study were inconclusive due to the small numbers of total deaths (N=163) and the relatively short time of observation, which ended on January 1, 1976. Since seven years of additional observation data were available and since the question regarding the long term health effects among workers occupationally exposed to PCBs is still unknown, an update to the original study was conducted to help provide more conclusive results.

For more details on the study population, on the two capacitor manufacturing facilities and on the levels of exposure to PCBs at the facilities studied, refer to the original report.¹ In general, the two facilities used similar manufacturing techniques. At Plant 1, PCBs were first used in 1946. The particular type of PCBs used, varied during the years from "Aroclor" (Monsanto trade name) 1254 (54% chlorine) to 1242 (42% chlorine) to 1016 (41% chlorine). During a survey conducted in 1977,¹ personal time weighted average exposures to PCBs (aroclor 1016) ranged from 24 $\mu\text{g}/\text{m}^3$ to 393 $\mu\text{g}/\text{m}^3$ at Plant 1. This survey was conducted shortly after changes in work practices and engineering controls were put into place, and after the use of PCBs was reduced to 25% of the 1976 level.⁷

At Plant 2, the use of PCBs started in 1938 and they also changed the type of PCBs from Aroclor 1254 to 1242 to 1016. During the 1977 survey the personal time weighted average exposures ranged from 381 $\mu\text{g}/\text{m}^3$ to 2120 $\mu\text{g}/\text{m}^3$ at Plant 2.

It is difficult to estimate past exposure to PCBs at either plant. However, Plant 1 had conducted area air sampling in 1975 and found exposure levels ranged from 260 $\mu\text{g}/\text{m}^3$ to 1160 $\mu\text{g}/\text{m}^3$ in areas of the large capacitor plant where PCBs were used.⁷ At the small capacitor site the exposure levels ranged from 360 $\mu\text{g}/\text{m}^3$ to 2000 $\mu\text{g}/\text{m}^3$ in areas where PCBs were used.

Methods

In the original study, the vital status of the cohort was determined as of January 1, 1976. This update extends the follow-up through December 31, 1982. The vital status follow-up was accomplished by searching the records maintained by the Social Security Administration, the Internal Revenue Service and the National Death Index (NDI). The NDI, which is administered by the National Center for Health Statistics, is a file containing information on all deceased individuals in the United States since 1979. For all those known to be deceased, death certificates were requested from the appropriate State Vital Statistics Office. The underlying cause of death listed on each death certificate was coded by a trained nosologist according to the Revision of the International Classification of Diseases (ICD) in effect at the time of death. Those lost to follow-up (unknown vital status) and those who died after December 31, 1982, were considered alive for purposes of analysis.

Person-years were accumulated for each worker, starting after three months of employment in "PCB exposed" jobs and ending at the date of death or the closing date whichever occurred first. Using a life table analysis system,⁸ the person-years for each worker were combined into 5-year calendar time periods and 5-year age groups and multiplied by the corresponding U.S. White Male (for male workers) and U.S. White Female (for female workers) cause-specific mortality rates to yield the expected number of deaths.

At the time of this analysis, the life table analysis system only maintained U.S. mortality rates through 1978, the end of the eighth revision of the ICD. To calculate expected deaths through 1982 for this study, the death rates for the interval 1975-1979 were based on U.S. deaths occurring through 1978, and the death rates for the interval 1980-1982, were assumed to be identical to the previous time period (1975-1979). Since the comparison rates did not include deaths occurring in the ninth revision of the ICD, deaths observed in the study population after 1978 were assigned codes according to the rules of the eighth revision of the ICD. This methodology could yield biased results if the U.S. death rates changed between 1978 and 1982. For liver cancer which was the cause of most concern, the death rates have remained constant.⁹

Person-years were additionally distributed by length of employment in "PCB exposed" jobs and by time since first employment in "PCB exposed" jobs (latency). The observed and expected cause-specific deaths were compared and differences were tested based on the Poisson distribution. The risk is reported as a standardized mortality ratio (SMR), defined as observed/expected deaths x 100.

Results

This update includes a slightly different total number of workers compared to the original cohort. There were 2567 workers in the original study and 2588 in the update. In the update 13 additional workers from Plant 1, and 8 additional workers from Plant 2 met the definition of the cohort and therefore were included.

The results of the vital status ascertainment through December 31, 1982 are given in Table 1. The update resulted in an additional 132 deaths and added 16,527 person-years to the original study.

Mortality by major cause of death is given in Table 2. Except for the category, "diseases of the circulatory system," which is slightly elevated (SMR=104), mortality from all other major causes is lower than expected. Compared to the original study, the change in SMRs for most of the major death groupings is minimal. The largest change is seen in malignant neoplasms where the SMR dropped from 89 (39 observed and 43 expected) to 78 (62 observed and 79.7 expected). This difference is due primarily to the observation of only one additional cancer death among Plant 1 males.

In Table 3 the mortality results by cancer site are given. Of particular interest are cancer of the rectum and cancer of the liver and biliary passages which were elevated in the original study, especially among females in Plant 2. No additional deaths from cancer of the rectum were observed since the

original study and the SMR dropped from 336 (4 observed vs 1.19 expected) to 211 (4 observed vs 1.9 expected). On the other hand, two additional deaths from cancer of the liver and biliary passages were observed, both among females in Plant 2. For the whole cohort, the SMR for this cause is 263 (5 observed vs 1.9 expected). The difference between these observed and expected deaths is statistically significant at $p < 0.05$ using a one-sided test of significance.

Since cancer associated with occupational exposure usually does not occur until many years after first exposure (latency), an analysis by this variable was conducted for cancer of the liver and biliary passages and is presented in Table 4. It does not appear that the risk is associated with time since first employment in "PCB exposed" jobs.

The risk from cancer of the liver and biliary passages was also examined by length of employment in "PCB exposed" jobs. This analysis is presented in Table 5. The pattern of risk does not resemble a typical dose response relationship, that is, it does not increase with an increase in exposure as measured by length of employment in "PCB exposed" jobs.

Both the latency and exposure analysis may be misleading because the two variables are measured in terms of employment in "PCB exposed" jobs only. These jobs were identified as those representing the heaviest and most direct exposure to PCBs and only account for approximately 10% of all jobs at the plants. As documented by industrial hygiene surveys,¹ there was potential

exposure throughout the plant; therefore, calculation of latency and exposure based on the workers' total employment at the plant may be more appropriate. For females from Plant 2, an analysis calculating observed and expected deaths stratified by length of employment and latency using total work history at the plant was conducted and is presented in Tables 6 and 7. Again, there is no apparent pattern of increasing risk with length of employment. All of the deaths occurred after 15 years of latency, although only 0.19 deaths were expected before 15 years.

In Table 8 additional information is provided for each of the deaths due to cancer of the liver and biliary passages. Two additional observations can be made from this information. First, all of these workers were first employed at the plants in the 1940's and early 1950's when exposures may have been at the highest levels. Second, the distribution of the specific type of liver and biliary system cancer is similar to that expected based on the mortality of the U.S. We found three out of the five deaths were from extrahepatic biliary tract cancer which includes gallbladder. Mortality from this category of disease is twice as common as primary liver cancer which includes hepatocarcinoma (hepatoma) and cholangiocarcinomas (intrahepatic bile duct).

Discussion

The most important finding of this updated study is the significant excess in cancer of the liver and biliary passages. This finding is of particular interest because it is consistent with animal studies where liver tumors have been induced by PCBs in several species of animals.²⁻⁶

The excess in mortality from cancer of the liver and biliary passages is primarily restricted to the female workers in Plant 2. This may be due to several reasons: (1) This group accounts for the largest segment of the total cohort - 41% of the person-years and 52% of the person-years over 20 years of latency. (2) Plant 2 airborne exposure levels to PCBs may have been higher during the time period included in the study (1938 to 1977) or the specific types of PCB mixtures used could have resulted in different kinds and amounts of exposure. However, it can not be determined directly whether the excess risk among the female workers is associated with higher exposures since historical exposure data are not available. (3) There may be differences other than exposure to PCBs that are related to the risk of developing liver cancer. The plant populations may differ in their alcohol consumption, dietary habits or ethnic makeup, all of which may have an affect on the risk for liver cancer mortality.¹⁰ This type of information was unavailable for analysis.

The analysis of liver cancer by length of employment and latency provides limited information concerning the association with exposure to PCBs, primarily because of the small numbers of deaths. Based on the four deaths from Plant 2, there is no clear increase in risk with increase in length of employment. The risk associated with latency is also uninformative, except no deaths occurred prior to 15 years from first employment. The date first employed among the liver cancer deaths is an important observation. They all began working during a time period when levels of exposure were probably the highest.

Since 1981 two other cohort mortality studies of workers exposed to PCBs have been reported. The first study, by Zack and Musch,¹¹ included workers who were involved in the manufacturing of PCBs. The study cohort was defined as all workers at the plant employed for at least six months during the period from 1945 to 1965. The cohort was followed through 1977. This study was limited, in that there were only 89 workers included in the cohort which yielded 30 deaths. There were no liver cancers but there were statistically significant increases in circulatory disease, exclusive of arteriosclerotic heart disease, in white males.

The second study, by Bertazzi et al.,¹² included 1310 workers employed for at least 6 months from 1946 to 1970 in a capacitor manufacturing facility located in Italy. Mortality of this cohort was determined from 1954 to 1978. In the original analysis of this data there were only 27 deaths, 14 of which were due to cancer. Two sites of cancer were elevated, digestive organs /peritoneum and lymphatic/hematopoietic. This study was recently updated through 1982 and was expanded to include all workers with at least one week of employment, increasing the cohort to 2100 workers.¹³ In the updated results there was a statistically significant excess in cancer (11 observed vs 5.3 expected) among females with a 3 fold excess (3 observed vs 1.1 expected) of lymphatic/hematopoietic cancer. Among males there was a statistically significant excess in all cancer (14 observed vs 7.6 expected) and in digestive cancer (6 observed vs 2.2 expected); and a non-significant excess in lymphatic/hematopoietic cancer (3 observed vs 1.1 expected). Unfortunately not enough information was given to determine the risk specifically for liver cancer.

The results from the studies of Zack and Musch and Bertazzi, et al. are limited by small numbers of death. At this time, neither study provides convincing evidence regarding the carcinogenicity of PCBs in occupationally exposed workers.

The update of this study provides limited information indicating that occupational exposure to PCBs is associated with an excess risk of mortality from cancer of the liver and biliary passages. One limitation to this study is the possible misclassification of cause of death reported on the death certificate. Based on information from the hospitals where the individual was treated, it is not clear in every case, that the cause of death was due to primary cancer of the liver or biliary passage, or whether the cancer was due to metastasis from another site. Additionally, because the number of deaths is small, definitive conclusions are still tentative. Continuing follow-up of this cohort as well as other cohorts exposed to PCBs should be encouraged.

Finally, this study illustrates the importance of periodically updating cohort mortality studies which are inconclusive due to small numbers of deaths and short latency periods. This is a fairly easy task since the demographic and work history data is already collected and computerized. For studies initially followed through 1978, only the National Death Index is necessary for determining the vital status of each cohort member.

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Table 1. Vital Status Ascertainment of Workers In PCB Cohort

	Plant 1			Plant 2			Grand Total (%)
	Males	Females	Total	Males	Females	Total	
Known Alive	508	341	849	587	758	1,345	2,194 (85)
Known Dead	80	36	116	61	118	179	295 (11)
Unknown	5	11	16	29	54	83	99 (4)
Total	593	388	981	677	930	1,607	2,588 (100)
Person-years	11,377	7,715	19,092	13,676	22,777	36,453	55,545

Table 2. Mortality* from Major Causes Among Workers In PCB Cohort

Cause of Death (7th Revision ICD No.)	Plant 1		Plant 2		Total	SMR [†]	SMR [‡] (observed)
	Males	Females	Males	Females			
All Malignant Neoplasms (140-205)	10/17.7	8/13.5	7/13.7	37/ 34.8	62/ 79.7	78	89 (39)
Nervous System (330-334,345)	2/ 5.0	2/ 3.6	4/ 3.4	12/ 10.6	20/ 22.6	88	88 (11)
Circulatory System (400-468)	43/36.9	15/13.5	30/26.6	32/ 38.6	120/115.6	104	95 (60)
Accidents (800-962)	8/ 8.3	3/ 1.8	6/10.4	4/ 5.3	21/ 25.8	81	71 (13)
All Other Causes	17/20.4	8/ 9.6	14/17.6	33/ 26.3	72/ 73.9	97	89 (40)
All Causes	80/88.3	36/42.0	61/71.7	118/115.6	295/317.6	93	89 (163)

* Mortality is reported as observed/expected deaths

† SMR = Observed/expected deaths x 100 - for the updated results

‡ SMR's from the original study. (observed deaths)

Table 3. Mortality (observed/expected deaths) From Malignant Neoplasms Among Workers In PCB-Cohort

Cause of Death (7th Revision ICD no.)	Plant 1		Plant 2		Total	SMR*	SMR [†] (observed)
	Males	Females	Males	Females			
All Malignant Neoplasms (140-205)	10/17.7	8/13.5	7/13.7	37/34.8	62/79.7	78	89 (39)
Stomach (151)	0/ 0.8	0/ 0.4	1/ 0.6	0/ 1.0	1/ 2.8	36	60 (1)
Intestine except Rectum (152, 153)	1/ 1.5	2/ 1.4	0/ 1.1	5/ 3.7	8/ 7.7	104	99 (4)
Rectum (154)	1/ 0.5	0/ 0.3	0/ 0.3	3/ 0.8	4/ 1.9	211	336 (4)
Liver and Biliary Passages [†] (155, 156 A)	1/ 0.4	0/ 0.3	0/ 0.3	4/ 0.9 [§]	5/ 1.9 [§]	263	280 (3)
Pancreas (157)	0/ 0.9	1/ 0.6	1/ 0.7	0/ 1.5	2/ 3.7	54	53 (1)
Respiratory (160-164)	5/ 6.3	2/ 1.7	0/ 4.8	3/ 4.1	10/16.9	59	88 (7)
Urinary (180-181)	2/ 0.9	0/ 0.3	2/ 0.7	0/ 0.9	4/ 2.8	143	not reported
Lymphatic and Hematopoietic (200-205)	0/ 1.8	0/ 1.1	1/ 1.6	4/ 2.9	5/ 7.4	68	46 (2)
Breast (170)	---	1/ 3.3	---	8/ 8.3	9/11.7	77	102 (7)
Female Genital Organs (171-176)	---	1/ 2.3	---	6/ 5.9	7/ 8.2	85	not reported
Other	0/ 4.6	1/ 1.8	2/ 3.6	4/ 4.8	7/14.8	---	---

*SMR's from updated study

[†]SMR's from the original study (observed deaths)

[†]Includes primary and unspecified as primary, liver and biliary passage cancer.

[§] Difference between observed and expected deaths is statistically significant $p < 0.05$, (one sided test of significance).

Table 4. Mortality From Liver Cancer by Time Since First Employed (latency) in "PCB Exposed" Jobs, For Total Cohort

Latency (years)	Plant 1		Plant 2		Total		SMR
	O	E	O	E	O	E	
< 10	1	0.2	1	0.2	2	0.4	500
10 - 19	0	0.2	1	0.4	1	0.6	167
≥ 20	0	0.3	2	0.6	2	0.9	222
Total	1	0.7	4	1.1	5	1.9	263

O = Observed deaths
E = Expected deaths

Table 5. Mortality From Liver Cancer by Length of Employment in "PCB Exposed" Jobs,
For Total Cohort

Length of Employment	Plant 1		Plant 2		Total		SMR
	O	E	O	E	O	E	
3 months < 5 years	1	0.5	3	0.8	4	1.3	308
<u>≥</u> 5 years	0	0.2	1	0.4	1	0.6	167
Total	1	0.7	4	1.2	5	1.9	263

O = Observed deaths
E = Expected deaths

Table 6 - Mortality From Cancer by Time Since First Employed (Latency) at Plant 2 Among Females

Latency Years	Observed Deaths	Expected Deaths
< 5	0	.04
5- 9	0	.06
10-14	0	.09
15-19	2	.13
20-24	0	.15
<u>≥</u> 25	2	.41
Total	4	.87

Table 7 - Mortality From Liver Cancer by Length of Employment at Plant 2 Among Females

Length of Employment (years)	Observed Deaths	Expected Deaths
< 5	2	.27
5- 9	0	.18
10-14	1	.15
15-19	0	.12
20-24	0	.10
<u>></u> 25	1	.05
Total	4	.87

Table 8 - Description of Liver and Biliary Passage Cancer Deaths in PCB Mortality Study

Plant	Sex	Date First Employed	Date of Death	Length of Employment	Cause of Death Code No. & Rev.	Cause of Death Notation On Death Certificate	Hospital/Pathology Report
1	MALE	<u>9/19/49</u> * <u>11/22/48</u>	11/28/58	<u>1 year</u> * <u>10 years</u>	155.0 7th Revision	Primary Carcinoma of Liver with Metastasis	Confirmed as intrahepatic bile duct cancer
2	FEMALE	<u>5/10/54</u> * <u>1/11/44</u>	1/23/62	<u>1.5 year</u> * <u>14.3 years</u>	155.1 7th Revision	Carcinoma of the biliary system	No reports available
2	FEMALE	<u>10/31/49</u> * <u>10/9/42</u>	3/6/79	<u>9.8 years</u> * <u>28 years</u>	156.0 8th Revision	Carcinoma of the gall-bladder	Adenocarcinoma of liver and gallbladder. Origin probably gallbladder, metastatic to liver.
2	FEMALE	<u>5/10/56</u> * <u>8/17/50</u>	7/21/79	<u>0.8 year</u> * <u>3.5 years</u>	156.1 8th Revision	Bile Duct Cancer	Cancer of the bile ducts. Origin probably from bile ducts. A history of cancer of the uterus.
2	FEMALE	<u>8/24/55</u> * <u>8/24/55</u>	8/23/70	<u>0.3 year</u> * <u>0.3 year</u>	197.8 8th Revision	Carcinoma of the liver	Hepatic coma due to hepatoma, due to metastatic disease - primary site unknown

*These dates and lengths of employment are based on total work history at the plant not restricted to "PCB Exposed" jobs.