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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. Based on animal data, liver cancer was the disease of most interest. Due to the small number of deaths and a relatively short observation period, the study was considered inconclusive. This study has been updated by adding 7 yr 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 vs. 318 expected deaths) as well as mortality from all cancers (62 observed vs. 80 expected deaths). A statistically significant excess in deaths was observed in the disease category that includes cancer of the liver (primary and unspecified), gall bladder, and biliary tract (5 observed vs. 1.9 expected; $p < .05$). Most of this excess was observed in women employed in one plant. Due to the small number of deaths and the variability of specific cause of death within this category, it remains difficult to interpret these findings in regard to PCB exposure.

IN 1981,[1] the results from a retrospective cohort mortality study of 2,567 workers employed in two plants where PCBs were used to manufacture electrical capacitors were 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 available at the time of the study,[2-7] and supported by more recent reports,[8,9] liver cancer was the disease of most concern. The study population included workers with at least 3 mo 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 7 yr of additional observation were available and since the question regarding the long-term health effects among workers occupationally exposed to PCBs remains unanswered, 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, the reader is

referred 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 $\mu g/m^3$–393 $\mu g/m^3$ at Plant 1. This survey was conducted shortly after changes in work practices and engineering controls were effected, and after the use of PCBs was reduced to 25% of the 1976 level.[10]

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 170 $\mu g/m^3$ to 1260 $\mu g/m^3$ 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 that exposure levels ranged from 260 $\mu g/m^3$–1160 $\mu g/m^3$ in areas of the large capacitor plant where PCBs were used. At the small capacitor site of Plant 1 the exposure levels ranged from 360 $\mu g/m^3$–2000 $\mu g/m^3$ in areas where PCBs were used.[10]

Since PCBs have a low vapor pressure and because the workers had frequent dermal contact with the compound, the airborne concentrations are probably a poor measure of the actual occupational exposure potential. To better estimate actual exposures, Lawton[11] measured PCB blood levels among workers at Plant 1 thought to have direct contact with PCBs and thus represented individuals selected similarly to those in the mortality study. This study population was examined in 1976 during PCB use and again in 1979, after PCBs were discontinued. In the 1976 survey the geometric mean serum level for Aroclor 1242 was 1470 ppb and for Aroclor 1254 it was 84 ppb. In the 1979 survey these levels fell to 277 ppb and 54 ppb for Aroclor 1242 and 1254, respectively. In contrast, control or background levels as measured among Connecticut office workers were 6.6 ppb and 14.4 ppb for Aroclor 1242 and 1254, respectively. No blood levels among Plant 2 workers were taken.

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 3 mo of employment in "PCB-exposed" jobs and ending at the date of death or the closing date of December 31, 1982, whichever occurred first. Using a life table analysis system,[12] the person-years for each worker were combined into 5-yr calendar time periods and 5-yr 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. To examine mortality by length of employment (a surrogate for exposure) and latency (time since first employment or exposure) the person-years were further distributed by these variables as well.

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 there were large enough changes in U.S. death rates between 1978 and 1982. For liver cancer, which was the cause of most concern, the death rates have remained constant.[13]

The observed and expected cause-specific deaths were compared and differences were tested based on the assumption that the observed deaths were distributed as a Poisson variable. The risk is reported as a standardized mortality ratio (SMR), defined as observed/expected deaths × 100.

For certain causes of death that were of interest in this study, additional information (e.g., pathology, autopsy, examination reports) was requested from the hospital and/or physician of the deceased case. The purpose of this information was to verify cause of death on the death certificate and to provide further information regarding the origin of the tumor and tumor type. However, this information was not used to change the underlying cause of death as coded by the nosologist and used in the statistical analysis.

Results

This update includes a slightly different total number of workers compared to the original cohort. There were 2,567 workers in the original study and 2,588 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.

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 of 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	118/11 5.6	295/317.6	93	89 (163)

*Mortality is reported as observed/expected deaths.
†SMR = observed/expected deaths × 100 for the updated results.
‡SMRs from the original study (observed deaths).

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, gall bladder, and biliary tract 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 the disease category that includes cancer of the liver, gall bladder, and biliary tract were observed, both among females in Plant 2. For the whole cohort, the SMR for this category is 263 (5 observed vs. 1.9 expected). The difference between these observed and expected deaths is statistically significant at $p < .05$ 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, gall bladder, and biliary tract 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 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 approximatley 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 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

Table 3.—Mortality (Observed/Expected Deaths) from Malignant Neoplasms among Workers in PCB Cohort

Cause of death (7th revision of 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	1/0.4	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, gall bladder, and biliary tract‡ (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	—	—	

*SMRs from updated study.
†SMRs from the original study (observed deaths).
‡Includes primary and unspecified as primary, liver, gall bladder, and biliary tract cancer.
§Difference between observed and expected deaths is statistically significant ($p < .05$, one-sided test of significance).

7. Again, there is no apparent pattern of increasing risk with length of employment. All of the deaths occurred after 15 yr of latency, which is somewhat consistent with the expectation of only 0.19 deaths before 15 yr.

In Table 8 further information is provided for each of the workers who died from cancer of the liver, gall bladder, and biliary tract. Two additional observations can be made from this information. First, all of these workers were first employed at the plants in the 1940s and early 1950s when exposures may have been at the highest levels and when the more highly chlorinated PCBs were used. Second, the distribution of the specific type of liver, gall bladder, and biliary tract cancer is similar to that expected based on the mortality of the U.S. We found three of the five deaths were from extrahepatic biliary tract cancer which includes gall bladder. 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 mortality from cancer of the liver, gall bladder, and biliary tract. This finding is of particular interest because in animal studies liver tumors have been induced by PCBs.[2-9] However, there is some inconsistency since the tumors induced in the animals were primary hepatocellular carcinomas; whereas the study population exhibited an excess risk in a broader category of tumor type and site. The analysis was limited to this broader category of deaths because the national mortality rates are maintained this way.

The observed excess risk from cancer of the liver, gall bladder, and biliary tract 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 total person-years and 52% of the person-years over 20 years of latency. (2)

Table 4.—Mortality from Liver, Gall Bladder, and Biliary Tract Cancer by Time since First Employed (Latency) in "PCB-Exposed" Jobs, for Total Cohort

Latency (yr)	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

Note: O = observed deaths and E = expected deaths.

Table 5.—Mortality from Liver, Gall Bladder, and Biliary Tract Cancer by Length of Employment in "PCB-Exposed" Jobs, for Total Cohort

Length of employment	Plant 1		Plant 2		Total		
	O	E	O	E	O	E	SMR
3 mo < 5 yr	1	0.5	3	0.8	4	1.3	308
⩾ 5 yr	0	0.2	1	0.4	1	0.6	167
Total	1	0.7	4	1.2	5	1.9	263

Note: O = observed deaths and E = expected deaths.

Table 6.—Mortality from Liver, Gall Bladder, and Biliary Tract Cancer by Time since First Employed (Latency) at Plant 2, among Females

Latency (yr)	Observed deaths	Expected deaths
<5	0	.04
5–9	0	.06
10–14	0	.09
15–19	2	.13
20–24	0	.15
⩾25	2	.41
Total	4	.87

Note: SMRs were not calculated because of the small numbers.

Table 7.—Mortality from Liver, Gall Bladder, and Biliary Tract Cancer by Length of Employment at Plant 2, among Females

Length of employment (yr)	Observed deaths	Expected deaths
<5	2	.27
5–9	0	.18
10–14	1	.15
15–19	0	.12
20–24	0	.10
⩾25	1	.05
Total	4	.87

Note: SMRs were not calculated because of the small numbers.

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. As a matter of fact, several different types of additives were used in the PCB mixtures. Some of these additives are potential carcinogens, such as epoxides.[14] However, these chemicals were added in very small quantities, 1% or less by weight, and the actual exposure to such compounds was probably very limited. In addition, there was a possibility of other contaminants in the PCB mixture such as trichlorobenzene, which was present primarily in the transformer fluids. Since the study cohort consisted mainly of workers involved in manufacturing capacitors, trichlorobenzene was not a serious confounding exposure. Unfortunately, it cannot be determined directly whether the excess risk among the female workers is associated with higher exposures or to contaminants because historical exposure data are not available. (3) There may be differences other than exposure to PCBs that are related to this risk. The plant populations may differ in their alcohol consumption, use of oral contraceptives, dietary habits, or ethnic makeup, all of which may have an effect on the risk for liver cancer mortality.[15] This type of information was unavailable for analysis. (4) If exposure to PCBs was responsible for the greater excess seen among the female workers, this may have been due to its sex-dependent carcinogenic promoting effect that has been observed experimentally in rats by Deml et al.[16] The investigators of this study indicate that the promoting effect of Clophen A 50 (a commercial PCB mixture) was stronger in female rats compared to male rats. The same effect has been observed in experiments involving Lindane and chlorobenzene and is thought to be related to the estrogenic activity of these substances or induction of estrogen metabolism by them. Since some estrogen hormones are known to be hepatocarcinogens, this could account for the sex-dependent effect.[16]

The analysis of liver, gall bladder, and biliary tract 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 yr 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, and when the more highly chlorinated PCB mixtures were being used. This is important since the animal data indicates that the higher chlorinated PCBs represent a greater carcinogenic potential compared to the less chlorinated compounds.[17–19]

Since 1981 three other cohort mortality studies of workers exposed to PCBs have been reported. The first study, by Zack and Musch,[20] included workers who

Table 8.—Description of Liver, Gall Bladder, and Biliary Tract Cancer Deaths in PCB Mortality Study

Plant	Sex	Date first employed	Date of death	Length of employment (yr)	Cause of death code No. & rev.	Cause of death notation on death certificate	Hospital/pathology report
1	Male	9/19/49* 11/22/48†	11/28/58	1* 10†	155.0 7th revision	Primary carcinoma of liver with metastasis.	Confirmed as intra-hepatic bile duct cancer —cholangiocarcinoma.
2	Female	5/10/54* 1/11/44†	1/23/62	1.5* 14.3†	155.1 7th revision	Carcinoma of the biliary system.	No reports available.
2	Female	10/31/49* 10/9/42†	3/6/79	9.8* 28†	156.0 8th revision	Carcinoma of the gall bladder.	Adenocarcinoma of liver and gall bladder. Origin probably gall bladder, metastatic to liver.
2	Female	5/10/56* 8/17/50†	7/21/79	0.8* 3.5†	156.1 8th revision	Bile duct cancer.	Adenocarcinoma; cancer of the bile ducts. Origin probably from bile ducts. A history of cancer of the uterus.
2	Female	8/24/55* 8/24/55†	8/23/70	0.3* 0.3†	197.8 8th revision	Carcinoma of liver.	Hepatic coma due to metastatic disease—primary site unknown.

*These dates and years of employment are based on time in "PCB-exposed" jobs only.
†These dates and lengths of employment are based on total work history at the plant not restricted to "PCB-exposed" jobs.

were involved in the production of PCBs. The study cohort was defined as all workers at the plant employed for at least 6 mo 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 was conducted by Gustavsson[21] and included both a mortality and incidence analysis of 142 male Swedish capacitor manufacturing workers. There was no excess in the observed number of cancer deaths or incident cases, however, the numbers of cases were much too small for a meaningful analysis. There were only 7 cancer cases in the total cohort and when a subgroup of higher exposed individuals was selected there were only 19 individuals who qualified for this analysis.

The third study was conducted by Bertazzi et al.[22] and included 1310 workers employed for at least 6 mo from 1946–1970 in a capacitor manufacturing facility located in Italy. Mortality of this cohort was determined from 1954–1978. 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 1 wk of employment, increasing the cohort to 2,100 workers.[23] In the updated results there was a statistically significant excess in cancer (12 observed vs. 5.3 expected) among females with an excess of lymphatic/hematopoietic cancer (4 observed vs. 1.1 expected). 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, gall bladder, and biliary tract cancer.

The results from these three studies are inconclusive primarily because of the small numbers of deaths. At this time, they do not provide 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 may be associated with an excess risk of mortality from cancer of the liver, gall bladder, and biliary tract. The limitations of this study include: (1) possible misclassification of the cause of death—based on the additional information available in the pathology/hospital reports, it is not clear in every case that the cause of death was due to primary cancer of the liver, gall bladder, and biliary tract; (2) the category of death found in excess includes cancer types that are different from those found in the animals exposed to PCB; therefore, the findings are somewhat inconsistent; and (3) the pattern of risk by latency and duration of employment is not completely consistent with that of an occupational carcinogen, which may be a function of the small number of deaths available for analysis. Because of these limitations, follow-up of this cohort as well as other cohorts of workers 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

relatively short periods of observation. 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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