

Mortality among Workers Exposed to Polychlorinated Biphenyls

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On the basis of evidence from animal studies, polychlorinated biphenyls (PCBs) are considered potentially carcinogenic to humans. However, the results of studies in human populations exposed to PCBs have been inconsistent. The authors conducted a retrospective cohort analysis (1957–1986) comparing the mortality of 3,588 electrical capacitor manufacturing workers with known exposure to PCBs with age-, sex-, and calendar time-specific mortality rates for all whites in the United States. Proportional hazards modeling was also performed to examine the association between cumulative PCB exposure and site-specific cancer mortality. All-cause mortality (192 deaths observed, 283.3 expected) and total cancer mortality (54 deaths observed, 63.7 expected) were lower than expected. More deaths were observed than expected for malignant melanoma (8 observed, <2.0 expected) and cancer of the brain and nervous system (5 observed, 2.8 expected). The average estimated cumulative dose for the cases of brain cancer (22.9 units) was greater than for other workers (12.9 units), but the 95% confidence intervals around this difference were broad. The risk of malignant melanoma was not related to cumulative PCB exposure. These results provide some evidence of an association between employment at this plant and malignant melanoma and cancer of the brain. The possibility that the results are due to chance, bias, or confounding cannot be excluded. *Am J Epidemiol* 1992;136:389–98.

brain neoplasms; electricity; melanoma; mortality; occupational diseases; polychlorinated biphenyls

Although banned from production and distribution in the United States, polychlorinated biphenyls (PCBs) remain in the environment. Exposed workers include those involved in the maintenance and replacement of electrical transformers and capacitors and those working in the disposal of materials containing PCBs (1). In 1985, the

Environmental Protection Agency estimated that 1.6 million substation capacitors and 21,000 transformers containing PCBs remained in use (2). Another two million mineral oil transformers were contaminated with PCBs at levels of >50 ppm. With approximately 2.5 percent of transformers removed from service annually, 1.4 million

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Abbreviations: CI, confidence interval; PCBs, polychlorinated biphenyls; SMR, standardized mortality ratio.

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contaminated transformers will remain in service in the year 2000.

On the basis of evidence from animal studies, PCBs are considered potentially carcinogenic in humans (3–5), but no consistent results have emerged from studies of humans exposed to PCBs. Some studies have found an excess of malignant melanoma, liver and biliary tract cancer, cancer of the rectum, hematopoietic malignancies, and lung cancer (6–9).

To further evaluate the carcinogenicity of PCBs, we conducted a retrospective cohort study of workers with known exposure to PCBs because they had worked in a plant that manufactured electrical capacitors containing PCBs (10).

MATERIALS AND METHODS

The study cohort consisted of individuals who worked at a plant in which electrical capacitors containing PCBs were manufactured from January 1957 through March 1977, at which time the PCBs were replaced with isopropyl biphenyl. Aroclor 1242 (Monsanto Chemical Company, St. Louis, Missouri) was used through 1970, and Aroclor 1016 was used from 1971 onward. The

plant was contained under a single roof with administrative offices and certain processing areas isolated by walls (figure 1). The details of the manufacturing process have been described elsewhere (10). The primary area in which exposure to PCBs occurred was the area around the impregnation ovens in which the capacitors were heated. When the doors of these ovens were opened, fumes were released, spreading PCBs throughout the facility.

Approximately 10 percent of the work force was directly involved in capacitor production. In 1977, the concentration of PCBs in the serum of workers in the plant was sevenfold greater for salaried workers and 50-fold greater for capacitor-processing workers than for individuals in the community (11). The solvents used at the plant included toluene, xylene, methyl ethyl ketone, trichlorethylene, and 1,1,1-trichloroethane. Personal and area environmental sampling for several metals indicated that metal exposures were well below the recommended standards.

Retrospective cohort study

The study cohort consisted of 3,588 men

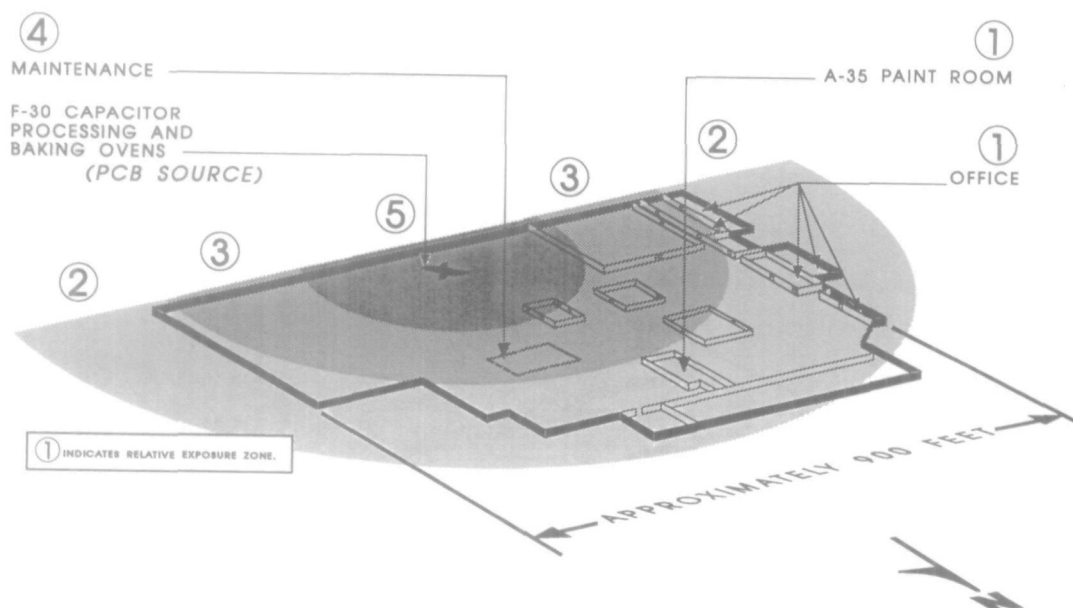


FIGURE 1. Floor plan of capacitor manufacturing plant showing impregnation ovens and polychlorinated biphenyl (PCB) exposure zones (900 feet = 274 m).

and women who worked at the plant for at least 1 day between January 1, 1957, when the plant opened, and March 31, 1977, when the use of PCBs was discontinued. All personnel records and death records in the company's possession were microfilmed and abstracted. Race was indicated in 12 percent of the personnel records, and the majority of these workers (96 percent) were white. We considered workers whose race was unknown to have been white, since 98 percent of the local population was white (12). Because of the small number of nonwhites in this cohort, we excluded persons known to be nonwhite from the analysis. Workers with missing dates of birth or Social Security numbers and those who had not worked for at least 1 day at the plant were also excluded.

Vital status was determined through the Social Security Administration. We received information on deaths reported to the Social Security Administration as of the end of 1987 and on persons known to be alive as of December 31, 1984. For persons who could not be traced by the Social Security Administration, the Internal Revenue Service provided both vital status and the mailing address of the most recent tax return. We considered these individuals alive if they were indicated to be so by the Internal Revenue Service and if the local post office confirmed that their mail was still being delivered. Vital status was considered unknown if it could not be determined from either the Social Security Administration or the Internal Revenue Service with post office follow-up.

Workers known to have been alive as of December 31, 1984, were assumed to be alive as of the study end date (June 30, 1986), unless they were known to have died. Those whose vital status was unknown and those who died after June 30, 1986, were considered alive in the life table analysis. For workers known to be deceased, the underlying cause of death was determined according to the revision of the *International Classification of Diseases* that was in effect at the time of death.

Person-years at risk of dying were accumulated starting on January 1, 1957, or on

the first day of employment at the plant, whichever occurred later, and continued until the date of death or the study end date (June 30, 1986), whichever occurred first. March 31, 1977, was considered the last possible day of employment. The Life Table Analysis System of the National Institute for Occupational Safety and Health was used to distribute person-years at risk over sex-specific 5-year calendar time periods and 5-year age groups (13). The expected numbers of cause-specific deaths were calculated by multiplying the age-, sex-, and calendar time-specific US mortality rates for all whites by the corresponding number of person-years at risk. The number of observed cause-specific deaths was divided by the number of expected cause-specific deaths to yield a standardized mortality ratio. Ninety-five percent confidence intervals around the standardized mortality ratio were calculated using an approximation based on the Poisson distribution (14).

Proportional hazards analysis

The primary purpose of the proportional hazards modeling (15) was to determine whether a dose-response relation existed between cumulative exposure to PCBs (duration of employment multiplied by an exposure intensity rating) and mortality from either malignant melanoma or brain cancer. Pertinent exposure information included our knowledge of the manufacturing process, environmental data collected in 1977 (10), and data on serum PCB levels collected during a cross-sectional study conducted a few months later (11) (table 1).

Our principal cumulative dose estimate (cumulative PCB 1) was based on the available environmental sampling results and the assumption that airborne and dermal PCB exposures decreased with distance from the impregnation ovens. We assigned the lowest exposure weight to the office area, giving it a weight of 1 and designating it as zone 1 (see figure 1). Two production departments, isolated by walls and separate ventilation systems, were also assigned to zone 1. The production area was then divided by three equidistant and concentric semicircles cen-

TABLE 1. Mean levels of polychlorinated biphenyls in a US electrical capacitor manufacturing plant and in serum samples from workers in the plant, 1977

		Zone							
		Unknown*		1		2		3	
		No.†	Level	No.	Level	No.	Level	No.	Level
<i>Environmental measurements ($\mu\text{g}/\text{m}^3$)</i>									
Area air sampling				2	16 \pm 15‡	4	48 \pm 13	8	59 \pm 19
Personal breathing zone sampling				0	NS§	0	NS	0	NS
<i>Serum samples¶ (ng/ml)</i>									
Current job									
Salaried workers		66	126 \pm 101						
Hourly workers only						51	199 \pm 377	23	98 \pm 45
Only worked in one area¶¶						71	305 \pm 479		
Salaried workers		36	119 \pm 26						
Hourly workers only						7	121 \pm 61	5	100 \pm 27
						8	763 \pm 1,117		

* Zone was unknown for salaried workers.

† No. of observations.

‡ Mean \pm standard deviation.

§ NS, not sampled.

¶ Serum levels of polychlorinated biphenyls were measured as lower chlorinated biphenyl molecules with no more than four chlorine atoms per molecule (8).

¶¶ Persons who only worked in this area during their employment

tered upon the impregnation ovens. A value of 5 (based on the environmental sampling data shown in table 1) was given to the highest exposure area immediately surrounding the ovens (zone 5). The process area furthest from the ovens was assigned an exposure weight of 2 (zone 2), and the area adjacent to the ovens was assigned a value of 3 (zone 3). Maintenance workers ($n = 34$) were assigned an exposure score of 4 (zone 4) if their primary work area was in zone 3 but they were called upon to work in zone 5. Hourly workers ($n = 125$) who could not be located by department were assigned to zone 2. Cumulative PCB 1 was calculated by multiplying the number of days worked in each department by its exposure weight, summing across departments, and dividing by the number of days in a year. Thus, cumulative PCB exposure from working in zone 5 for 1 year was considered equivalent to that from working in zone 1 for 5 years.

Since the accuracy of our estimate of cumulative PCB could not be verified, we estimated it using two additional weighting schemes. Our second estimate (cumulative

PCB 2) was based on the results of the serum PCB values, assigning a weight of 1 to zones 1–4 and a weight of 5 to zone 5. The third estimate (cumulative PCB 3) assumed no exposure difference in zones 2–4, which were weighted by a factor of 2.5. Zone 1 and zone 5 retained their original weights.

We examined several exposure variables besides cumulative PCB dose. Workers were categorized as exposed (or not exposed) to 1,1,1-trichloroethane, trichloroethylene, toluene, methyl ethyl ketone, and xylene if they had worked in a department where these solvents were detected during environmental sampling. Work in each PCB exposure zone (dichotomous) and ever having worked outside of zone 1 were also analyzed. We also examined the duration of employment and years since first employment. We did not consider exposure to the various metals, because the environmental measurements indicated that these exposures were minimal.

Cases for the proportional hazards analysis included workers from the population at risk with a primary cancer of the brain or a

malignant melanoma listed as an underlying or contributory cause of death. Age was used as the time variable. Cases whose illness was diagnosed before their employment began were excluded. All workers who were born within 5 years of a case and were the same sex as the case were eligible for inclusion in a comparison group (risk set) for that case. The risk sets were further limited to workers who survived to the age at which the case died and were employed at the facility prior to that age. The work history of each member of the risk set was truncated at the age at which the index case had died.

An association between cumulative dose of PCB exposure and cancer outcome was considered to exist if 95 percent confidence intervals surrounding the risk estimate for cumulative dose did not include 1.0. Ninety-five percent confidence intervals were calculated for the estimated rate ratios using a test-based method proposed by Miettinen (16). Variables that, when included in the model, altered the coefficient representing PCB exposure were maintained for multivariate analysis. All two-way interactions were examined.

RESULTS

Retrospective cohort study

The study cohort included 3,588 workers—2,742 men and 846 women (table 2). Overall mortality was lower than expected (192 deaths observed; standardized mortality ratio (SMR) = 0.7, 95 percent confidence interval (CI) 0.6–0.8), as was mortality from diseases of the heart (60 deaths observed; SMR = 0.7, 95 percent CI 0.5–0.9) and accidents (28 deaths observed; SMR = 0.7, 95 percent CI 0.5–1.0) (table 3). The standardized mortality ratio for all cancers was also below that expected (54 deaths observed; SMR = 0.8, 95 percent CI 0.6–1.1). The standardized mortality ratio for deaths due to skin cancer was elevated (8 deaths observed; SMR = 4.1, 95 percent CI 1.8–8.0). All eight skin cancer deaths were due to malignant melanoma. (The Life Table of the National Institute for Occupational Safety and Health does not contain a calcu-

TABLE 2. Sex and vital status of workers exposed to polychlorinated biphenyls in a US electrical capacitor manufacturing plant, 1957–1977

Factor	Total no.	No. rejected	No. in final cohort
Sex*			
Male	2,785	43	2,742
Female	858	12	846
Total	3,643	55†	3,588
Vital status			
Alive	3,288	47	3,241
Deceased	216	7	209‡
Unknown	139	1	138§
Total	3,643	55	3,588

* Persons of unknown race (88 percent) were included as white.

† Rejected from the analysis because their work histories did not meet study inclusion criteria ($n = 40$) or their race was known to be nonwhite ($n = 15$).

‡ Seventeen workers died after June 30, 1986, and were considered alive as of the study end date (June 30, 1986).

§ Workers with an unknown vital status ($n = 138$; 3.8 percent) were considered alive as of the study end date (June 30, 1986).

lation for the expected number of deaths from malignant melanoma.) An increase was also noted for death from cancer of the brain and nervous system (5 deaths observed; SMR = 1.8, 95 percent CI 0.6–4.2). The excess mortality from melanoma and brain cancer affected both men and women.

All eight melanoma deaths included in the life table analysis occurred 5 or more years after initial employment, and three deaths occurred in individuals who had worked at the plant for more than 10 years (table 4, top). One person had been diagnosed with malignant melanoma approximately 2 months prior to working at the facility. The observed excess skin cancer mortality remained after this case was removed from the life table analysis (SMR = 3.5, 95 percent CI 1.4–7.3). A ninth worker died in 1987 with malignant melanoma listed as a contributory cause of death; this individual had worked at the plant for 1 month and died 20 years after exposure. Pathology reports or medical records confirmed the diagnosis of malignant melanoma for all cases.

All five brain cancer deaths included in the life table analysis occurred 5 or more years after the date of hire, and were more

TABLE 3. Observed and expected numbers of deaths and standardized mortality ratios for 3,588 electrical capacitor workers exposed to polychlorinated biphenyls, 1957-1977

Underlying cause of death	Obs†	Exp†	SMR†	95% CI†
All causes	192	283.3	0.7**	0.6-0.8
All cancers	54	63.7	0.8	0.6-1.1
Site-specific cancers				
Buccal cavity and pharynx	0	1.7		
Digestive organs	8	13.9	0.6	0.2-1.1
Biliary passages, liver, and gallbladder	1	0.8	1.1	0.0-6.4
Pancreas	2	2.8	0.7	0.1-2.5
Rectum	1	1.2	0.8	0.0-4.5
Respiratory system	15	20.2	0.7	0.4-1.2
Kidney	2	1.5	1.3	0.2-4.8
Lymphatic and hematopoietic tissue	7	7.2	1.0	0.4-2.0
Skin‡	8	2.0	4.1**	1.8-8.0
Brain and nervous system§	5	2.8	1.8	0.6-4.2
All other sites combined	5	8.5	0.6	0.2-1.4
Diseases of the heart	60	85.4	0.7**	0.5-0.9
Diseases of the respiratory system	10	12.3	0.8	0.4-1.5
Accidents	28	41.1	0.7*	0.5-1.0
Violence	14	21.5	0.6	0.5-1.1

* $p < 0.05$; ** $p < 0.01$.

† Obs, observed; Exp, expected; SMR, standardized mortality ratio; CI, confidence interval.

‡ The expected number of deaths was calculated using mortality rates for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma combined. All observed skin cancer deaths were due to malignant melanoma.

§ Cancer of the brain and central nervous system included the following *International Classification of Diseases* codes: code 193, Sixth and Seventh Revisions; and codes 191 and 192, Eighth and Ninth Revisions.**TABLE 4. Mortality from skin cancer and cancer of the brain and central nervous system in 3,588 electrical capacitor workers exposed to polychlorinated biphenyls, by duration of employment and number of years since first employment, 1957-1977**

Years since first employment		Duration of employment (years)		
		<10	≥10	Total
<i>Skin cancer*</i>				
<10	O/E†	2/0.56		2/0.56
	SMR†	3.59		3.59
≥10	O/E	3/1.01	3/0.43	6/1.44
	SMR	2.97	6.98	4.16
Total	O/E	5/1.57	3/0.43	8/1.99
	SMR	3.19	6.98	4.02
<i>Cancer of the brain and central nervous system‡</i>				
<10	O/E	2/0.88		2/0.88
	SMR	2.28		2.28
≥10	O/E	0/1.29	3/0.62	3/1.91
	SMR	0.00	4.84	1.57
Total	O/E	2/2.16	3/0.62	5/2.79
	SMR	0.92	4.84	1.79

* Expected numbers of skin cancer deaths were calculated for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma combined. All observed skin cancer deaths were due to malignant melanoma.

† O/E, observed/expected; SMR, standardized mortality ratio.

‡ Expected numbers of cancers of the brain and central nervous system included the following *International Classification of Diseases* codes: code 193, Sixth and Seventh Revisions; and codes 191 and 192, Eighth and Ninth Revisions.

common among those with a longer duration of employment (table 4, bottom). Two additional brain cancer deaths were observed that were not included in the life table analysis. One worker died of a glioblastoma shortly after the study end date. He had worked at the plant for 6 months and died 24 years after his first exposure. A black female who had worked at the plant for 11 years died of a glioblastoma 2 years after leaving work. Pathology records or medical records confirmed the diagnosis of primary brain cancer in the five workers who had died of brain cancer. Medical records could not be obtained for two of the cases, but death certificates indicated that the underlying cause of death was carcinoma of the brain.

Proportional hazards analysis

The proportional hazards analysis for malignant melanoma included eight cases with risk sets that varied in size from 111 to 1,112 workers. The distributions of the cases and their comparison groups by exposure zone were similar, with 25 percent of the cases and 33 percent of the comparison group ever having worked in zone 5. Only one case worked in a department that had been monitored for solvents. The 95 percent confidence intervals surrounding the odds ratios for years since first employment, duration of employment, and cumulative PCB exposures all included 1.0 (table 5).

The proportional hazards models for brain cancer included seven cases, and the risk sets varied in size from 42 workers to 489 workers. Cases were more likely than the comparison group to have worked in zone 3 (rate ratio = 3.4, 95 percent CI 0.7–16.8). Only one case was considered potentially exposed to any of the solvents. The number of years since first employment was similar between the cases and their comparison group. Brain cancer cases had a longer average duration of employment than the comparison group, but the 95 percent confidence interval for this association was broad (table 5). Of the three measures of cumulative exposure, the two estimates that

TABLE 5. Mean values for number of years since first employment, duration of employment, and estimated cumulative exposure among electrical capacitor workers exposed to polychlorinated biphenyls, and rate ratios for mortality from malignant melanoma or brain cancer according to these variables, 1957–1986

	Malignant melanoma					Brain cancer				
	Cases (n = 8)		All risk sets combined (n = 3,455)			Cases (n = 7)		All risk sets combined (n = 1,670)		
	Mean	SD*	Mean	SD	RR†, ‡	95% CI*	Mean	SD	Mean	95% CI
Years since first employment	14.5	6.5	13.5	6.8	1.16	0.21–6.48	14.1	6.1	14.9	7.5
Duration (years) of employment	4.5	4.5	4.6	5.5	0.82	0.22–3.03	8.8	6.5	5.2	5.7
Estimated cumulative PCB* exposure†										
Cumulative PCB 1	8.2	11.9	10.8	14.9	0.83	0.47–1.44	22.9	22.0	12.0	15.8
Cumulative PCB 2	7.3	10.6	7.2	11.3	0.97	0.50–1.88	14.2	16.4	8.3	12.7
Cumulative PCB 3	8.6	12.5	10.9	15.1	0.85	0.50–1.46	21.8	20.4	12.1	16.1

* SD, standard deviation; RR, rate ratio; CI, confidence interval; PCB, polychlorinated biphenyl.

† The rate ratios presented estimate the risk associated with any 10-unit increase in these continuous variables, as calculated by a Cox proportional hazards model.

‡ Cumulative PCB 1, estimate of cumulative PCB dose based on duration weighted by distance from impregnation ovens.

Cumulative PCB 2, estimate of cumulative PCB dose based on duration with a weight of 5 for days worked in zone 5.

Cumulative PCB 3, estimate of cumulative PCB dose based on duration with a weight of 1 for days worked in zone 1, a weight of 2.5 for days worked in zones 2–4, and a weight of 5 for days worked in zone 5.

weighted departments by proximity to the impregnation ovens (cumulative PCB 1 and cumulative PCB 3) were stronger predictors of brain cancer. On average, brain cancer cases had more than twice the estimated cumulative PCB dose (cumulative PCB 1) of the comparison group, but again, the 95 percent confidence interval for this association was broad.

DISCUSSION

This group of workers had an overall survival rate that was better than expected when they were compared with all white men and women in the United States. At the same time, they experienced greater than fourfold excess mortality from malignant melanoma. The risk for malignant melanoma did not vary by duration of employment, time since first employment, or estimated cumulative PCB exposure. There was also an excess of brain cancer mortality which increased with duration of employment. The workers who died of brain cancer had a higher cumulative PCB exposure than the other workers at the plant. However, the 95 percent confidence intervals for these measures of brain cancer risk were broad, and the results should be interpreted with caution.

Predisposing risk factors (17) or environmental exposures probably do not account for the excess deaths reported in this study. Interviews were conducted with the next of kin of the eight workers who had died of malignant melanoma. None of the cases were related to each other, none had a congenital mole, and none had had an earlier primary malignant melanoma. One case may have had a dysplastic mole; two were considered sun-sensitive; and one was of Celtic ancestry. An environmental cause is also unlikely. Age-adjusted and calendar time-specific mortality rates (18) for malignant melanoma and brain cancer for the county where the facility was located were similar to both state and national rates.

The skin is a recognized target organ for several effects of PCBs, and it is a major route of exposure in the workplace. Chloracne (19–21) and hyperpigmentation (22)

have been reported among PCB-exposed workers. While PCBs appear to affect melanocytes, it is not known whether they promote or initiate neoplastic transformation in these cells, and the mechanisms involved in hyperpigmentation and carcinogenesis probably differ.

Studies of human populations exposed to PCBs have yielded a variety of results. No excess cases of brain cancer or malignant melanoma were reported in three cohort studies (7, 9, 23). An excess incidence of malignant melanoma was reported in a cohort of 72 workers exposed to PCBs (6), but that study was considered inconclusive (24). Excess numbers of brain cancer cases have been found in two other PCB-exposed cohorts (8, 25). Unrecognized differences between study populations, different exposures from different manufacturing processes, exposures to other carcinogens, or chance may explain the discrepancies between the various studies. At the same time, the statistical power (26) of all of these studies has been limited by the relatively small numbers of deaths observed.

Our study had several limitations. Fewer than 10 percent of the person-years at risk were calculated with more than 19 years since the date of hire, and there have been relatively few deaths in this cohort. Thus, we could not assess the risk of cancers with long latency periods. In addition, the small number of observed deaths resulted in risk estimates with broad confidence intervals.

The manner in which the environmental and biologic exposure data were collected is perhaps the greatest limitation of this study. The small number of environmental samples collected outside the capacitor processing area and the lack of any data from before 1977 prevented the construction of a validated job-exposure matrix. The data from serum PCB measurements, also collected at a single point in time, only included information on current employees. Furthermore, the concentration of PCBs in serum is affected by their long half-lives (27) and by individual factors such as body weight, age, and sex (11), which further limits the usefulness of these data. Because of these limi-

tations, the weighting scales used must be considered crude approximations. While other weighting scales can be envisioned, all incorporate assumptions that cannot be adequately tested. Thus, the limitations of the exposure data may have led to substantial misclassification, obscuring a possible dose-response relation (28).

Various forms of bias or confounding should also be considered. The healthy worker effect (29), together with the inclusion of persons lost to follow-up, could partly explain the low overall mortality of this cohort. A small selection bias came about from our decision to exclude from the life table analysis four nonwhites whose race was determined from death certificates. At the same time, a small amount of person-time for unidentified, surviving nonwhites slightly increased the expected numbers of deaths. Finally, any association of excess mortality with PCBs may have been confounded by simultaneous exposure to PCB contaminants, such as polychlorinated dibenzofurans, or other unidentified substances.

Despite the conflicting results from the various epidemiologic studies, PCBs are considered potentially carcinogenic to humans by the National Institute for Occupational Safety and Health (3), the International Agency for Research on Cancer (4), and the Environmental Protection Agency (5). This study provides some evidence of an association between PCB exposure in an occupational environment and mortality from malignant melanoma. The brain cancer finding suggests that this outcome should be carefully studied in further follow-up of this cohort. The continued follow-up of this cohort and several other large cohorts of PCB-exposed populations will be essential for the final determination of the carcinogenicity of PCBs to humans.

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