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Cancer Mortality of Capacitor Manufacturing Workers

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Experimental studies have demonstrated that certain types of commercially produced polychlorinated biphenyls (PCBs) are carcinogenic. Data in humans are still controversial. This study was undertaken in order to determine possible long-term effects, particularly cancer, in workers engaged in the manufacture of capacitors impregnated with PCBs in a plant operating since 1946. All workers employed for at least 1 week between 1946 and 1978 were admitted to the study (544 males and 1,556 females), and their mortality was examined for the period 1946–1982. Data on environmental contamination, workers' PCBs intake, and health effects (chloracne) were available, which documented the general exposure conditions in the plant. Vital status was ascertained for over 99% of the subjects, and death certificates were obtained for all deceased persons. Expected deaths were calculated using two sets of mortality rates, national and local. Among male workers, cancer deaths (14 obs.) were significantly increased as were deaths owing to cancer of the gastrointestinal (GI) tract (6 obs.). Also, mortality from hematologic neoplasms (3 obs.) and lung cancer (3 obs.) was higher than expected; however, the excess was statistically not significant. Female workers exhibited an overall mortality that was significantly increased above expectations. Cancer deaths (12 obs.) and hematologic neoplasms (4 obs.) were significantly higher than expected when compared with the local population. Interpretation of the results is limited by the small number of deaths; however, the point of interest is the consistency of these results with previous experimental and epidemiologic studies, which indicated the GI tract and lymphatic and hemopoietic tissue as the most probable target sites of the PCBs carcinogenic activity.

Key words: PCBs, chemical carcinogenesis, occupational cancer, mortality, occupational epidemiology, hematologic neoplasms

INTRODUCTION

Polychlorinated biphenyls (PCBs) were introduced in industrial production at the beginning of the 1930s. Their manufacture increased progressively in succeeding decades, and their use, at least until the 1970s, became more and more widespread in various industrial sectors, enough to create contamination problems not only in the work place but also in the general environment [Interdepartmental Task Force on PCBs, 1972].

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The first data on the human toxicity of chlorinated compounds go back to the 1930s [Schwartz, 1936; Schwartz and Barlow, 1942] when the first cases of chloracne were reported in workers exposed to a variety of compounds including PCBs and chlorinated naphthalenes. However, the real toxic power of these compounds was fully appreciated for the first time only in 1968 when, in Japan, more than 1,000 people were accidentally poisoned (Yusho syndrome) after eating rice contaminated by a mixture of PCBs, which contained polychlorinated dibenzofurans (PCDFs) and quaterphenyls (PCQs) as impurities. Other than the already known cutaneous effects, hepatic, metabolic, neurological, and reproductive damage was noted [Kuratsune, 1976]. Analogous effects were reported following a very similar accident in 1979 in Taiwan, in which almost 2,000 people were struck by food poisoning [Hsu et al, 1984]. The multiform toxic action of PCBs has been documented in numerous experimental studies, without however, identifying a specific pathogenic mechanism.

A number of studies since 1972 have reported evidence of a carcinogenic effect in different species of animals. Nagasaki et al [1972] first, and then Ito et al [1973] observed, after administering different doses of Kanechlor 300, 400, and 500 in the diet of mice (100, 250, and 500 ppm) for 32 weeks, the onset of hepatocellular carcinomas in 5 of the 12 animals given the highest dose. Liver hepatomas and adenofibromas were observed by Kimbrough and Linder [1974] after feeding mice 300 ppm of Aroclor 1254 for either 6 or 11 months. Kimbrough et al [1975] also observed liver cell carcinomas and neoplastic nodules in rats given Aroclor 1260 in their diet. In an NCI study [1977], doses of 25, 50, and 100 ppm of Aroclor 1254, administered orally to rats for 104 weeks, gave rise to lymphomas, leukemias, hyperplastic hepatic nodules, and adenocarcinomas of the stomach. The comparison with the control groups, however, did not show statistically significant differences, and the study was considered inconclusive as to the carcinogenic properties of PCBs.

Studies of the metabolic fate of these substances in animals sustain the plausibility of a carcinogenic action. At least for some of these compounds (tetra-CB), the process of in vivo degradation occurs through the formation of intermediate metabolites (arene oxides) endowed with electrophilic properties and capable, therefore, of binding nucleophilic sites of cellular macromolecules [Allen and Norback, 1977]. The penta- or hexa-CB would behave similarly after a dechlorination process. On the basis of these data, the International Agency for Research on Cancer [1978] deemed sufficient the evidence of carcinogenicity of PCBs in experimental animals.

Notwithstanding the absence of a systematic follow-up, the study of the causes of death among the Yusho patients exposed to PCBs and PCDFs showed an excess of malignant tumors from such exposures; the sites mostly affected were the gastrointestinal (GI) tract and lymphatic and hematopoietic tissue [Urabe et al, 1979]. A suggestive excess of melanoma and possibly pancreatic cancer had been described in a group of workers with intense occupational exposure to PCBs [Bahn at al, 1976]. Subsequently, the mortality of two cohorts of workers involved in manufacturing electrical capacitors was studied, and an excess of deaths from hepatic and rectal tumors, although statistically not significant, was observed [Brown and Jones, 1982].

Evidence of the carcinogenicity of PCBs for man was still considered inadequate in the revision made by the International Agency for Research on Cancer [1982]. Recent reports [Wright et al, 1982; McDowall, 1983] have brought to light an increased mortality from leukemia among workers in the electrical industry; as an explanation, possible exposure to PCBs was suggested. By the same token, the high

frequency of melanomas observed in office workers was possibly related to such exposure [Jensen, 1982] in environments with atmospheric concentrations of PCBs 50–80 times higher than those measured in the external environment [Digernes and Astrup, 1982].

The most systematic study [Umeda, 1984] conducted in these years on causes of death in Yusho patients (522 males and 487 females) confirmed the existence of a statistically significant excess of deaths from malignant tumors (SMR = 165) and reported six cases of primary carcinomas of the liver (SMR = 492).

The preliminary results of a study of a cohort of Italian workers in capacitor production suggested an increased mortality from cancer of the GI tract and the lymphatic and hemopoietic tissue [Bertazzi et al, 1982]. In the present study, the mortality of this cohort was further examined in the period 1946–1982.

MATERIALS AND METHODS

Plant Description

The factory, situated in a highly industrialized city of about 150,000 inhabitants north of Milan, has produced, but did not repair, small capacitors for electrical and electronic use and large power capacitors impregnated with PCBs since 1946. Until 1964, mixtures containing 54% chlorine (Aroclor 1254 and Pyralene 1476) were utilized. Since 1965, they were progressively replaced by mixtures containing 42% chlorine (Pyralene 3010, 3011), until 1970 when only the latter were utilized. The maximum quantities of PCBs were used in 1967–1968, with an annual consumption of approximately 250 tons. Since 1980, the use of PCBs has been completely abandoned, and they have been replaced with other dielectric fluids. Other exposures in the plant were limited. Solvents (trichloroethylene) were used in the final step of the manufacture, in a protected area with efficient ventilation. In the manufacture of particular types of capacitors, alkylbenzene and epoxy resins were used; however, few individuals were involved in this kind of production.

Exposure Evaluation

Data on environmental contamination or on exposure in the initial years of the plant were not available. However, in 1954, three cases of chloracne were reported, which occurred among autoclave operators after, respectively, 4, 6, and 7 months from the beginnning of the exposure. At that point, three environmental air samples were taken, and the values of Aroclor 1254 reported were 5,200 $\mu g/m^3$, 6,400 $\mu g/m^3$, and 6,800 $\mu g/m^3$ [Puccinelli, 1954]. In 1977 and 1982, further investigations were carried out. Owing to cost and feasibility reasons, only a limited number of workers were examined, who were selected as representative of the "typical" exposure conditions in the plant. Thus, results could only provide a general, qualitative picture of the exposure without allowing a description of the quantitative individual exposure of each worker.

In 1977, among 67 workers examined, four cases of chloracne were diagnosed. All cases had been engaged in impregnating capacitors with PCB. The reported airborne concentrations of Pyralene 3010 (area samples) ranged between 48 $\mu g/m^3$ and 275 $\mu g/m^3$ [Maroni et al, 1981a,b].

Given the importance of skin absorption as a route of exposure, the total quantity of PCBs deposited on workplace surfaces and on workers' hands was measured in

1977 and 1982, according to the same analytical method [Ferioli et al, 1979]. Results of the successive investigations are reported in Table I. Skin contact was confirmed as a major exposure route. Despite a significant diminution of values, a notable degree of contamination still persisted in 1982. PCBs were also measured in the blood of the same 37 workers at these two points in time (Table II). It was evident that PCBs with 54% chlorine content persisted longer in the body than the mixture with 42%: the mean concentration of the former was in fact only slightly lowered in 1982, 3 years after discontinuing the use of the compounds. In order to interpret these values, consider that blood concentration estimated in the occupationally unexposed general population was less than 30 ppb [Doguchi and Fukano, 1977; Finklea et al, 1972; Ouw et al, 1976; Baker et al, 1980], and even less than 15 ppb in Italy [Ferioli et al, 1982]. On the other hand, levels of environmental contamination and blood concentrations in this working population were comparable with those reported in analogous studies [Karppanen and Kolho, 1973; Wolff, 1978; Wolff et al, 1982; Smith et al, 1982].

Population

In our previous study [Bertazzi et al, 1982], only workers in the production department were examined. Since, however, different departments and production areas (including administration) were located in a single building, contaminated surfaces were discovered in the whole plant, and nonproduction workers were admitted into this study. In addition, a minimum length of employment of 1 week was sufficient for admission, contrary to the 6-month requirement of the previous study. The reason for that was twofold: 1 week was the minimum period of employment necessary to obtain reliable data on an employee; chloracne cases described in a previous study [Puccinelli, 1954] showed that less than six months employment could result in substantial exposure to PCBs. Thus, all male and female workers who had

TABLE I. Minimum and Maximum Values of PCBs Recovered From Workplace Surfaces and Workers' Hands Before and After PCBs Banning (1980) and Cleaning Operations

			Values ($\mu g/cm^2$)	
	Year	No. samples	Min	Max
Workplace surfaces	1977	18	.2	159
	1982	14	.003	6.3
Workers' hands	1977	9	.3	9.2
	1982	12	.09	1.5

TABLE II. Mean Concentration and Standard Deviation (SD) of PCBs in the Blood of the Same 37 Workers Examined Before and After PCBs Banning (1980) and Cleaning Operations

Type of PCBs	Year	Mean (ppb)	SD (ppb)
54% chlorine content	1977	282.8	163.4
	1982	202.8	111.7
42% chlorine content	1977	142.8	74.5
	1982	42.9	34.7

worked between 1946 and 1978 for at least 1 week in the plant were included in the study. The personnel office supplied the following information for every worker: first and last name, sex, date and place of birth, residence, and dates of hire and resignation. Detailed work histories were only available for workers hired in recent years. Therefore, specific job description could not be considered in the analysis.

Analysis

Mortality was examined for the period 1946–1982. For workers no longer at the factory, vital status was ascertained at the Vital Statistics Bureau of the place where they resided or were born; causes of death were obtained from death certificates. Persons not traced were assumed to be alive at the end of the study. The analysis was conducted with a computer program specifically developed for these types of studies [Zocchetti and Bertazzi, 1982]. Each subject contributed to the person-years at risk from the moment he or she reached the minimum defined exposure (1 week) until the end of the study (12.31.1982) or, if deceased, until the date of death. The expected deaths were calculated using two sets of mortality rates (nation and city where the plant is located) subdivided by cause, sex, age (5-year periods), and calendar time (5-year period). The ratio of observed to expected deaths $\times$ 100 was calculated (SMR) with 95% confidence limits according to the Miettinen method [Rothman and Boice, 1979].

RESULTS

There were 2,100 workers (544 males and 1,556 females) admitted to the study, making a total of 41,010 person-years. Population status at the end of the follow-up is given in Table III; ten subjects, fewer than 1% of the participants, were not traced.

Overall mortality among male workers did not differ from expectations (Table IV), but deaths owing to cancer were significantly higher than expected according to either the national or the local population mortality rates. Of the 14 tumors observed, six were of the digestive tract (two stomach, two pancreas, one liver, and one biliary tract), a number significantly higher than expected. Mortality owing to hematologic neoplasms was also higher than expected; however, the number of cases was small, and the excess was not statistically significant. Even the three cases of death from lung cancer were more than expected, but not significantly so. Neither cardiovascular mortality nor deaths owing to external causes differed noticeably from expectations.

Contrary to what was noted among males, SMRs in female workers were higher when local rather than national rates were used in calculating expected deaths (Table

TABLE III. No. of Workers Admitted Into the Study, Their Status at the End of the Follow-Up, and Total No. of Person-Years Accumulated During the Study Period

Status	Males (%)	Females (%)
Admitted in the study	544 (100)	1,556 (100)
At the end of the study:		
Alive	509 (93.6)	1,517 (97.5)
Dead	30 (5.5)	34 (2.2)
Not traced	5 (.9)	5 (.3)
Person-years	10,307	30,703

TABLE IV. Mortality From Selected Causes of Male Workers Exposed to PCBs

Cause of death (ICD 8th revision)	Observed	Reference mortality: National Expected	National SMR	Local Expected	Local SMR
All causes	30	27.8	108	29.8	101
Malignant tumors (140–209)	14	5.5	253[a]	7.6	183[b]
Cancer of GI tract (150–159)	6	1.7	346[c]	2.2	274[d]
Lung cancer (162)	3	1.2	250	1.6	187
Hematologic neoplasms (200–209)	3	.8	375	1.1	263
Cardiovascular disease (390–458)	8	7.9	101	9.4	95
Accidents (800–999)	6	6.8	88	5.8	103

[a][Confidence limits 95% =] 144–415.
[b][Confidence limits 95% =] 104–300.
[c][Idem] 141–721.
[d][Idem] 112–572.

TABLE V. Mortality From Selected Causes of Female Workers Exposed to PCBs

Cause of death (ICD 8th revision)	Observed	Reference mortality: National Expected	National SMR	Local Expected	Local SMR
All causes	34	25.8	132	16.5	206[a]
Malignant tumors (140–209)	12	7.7	156	5.3	226[b]
Hematologic neoplasms (200–209)	4	1.5	266	1.1	377[c]
Cardiovascular disease (390–458)	2	4.7	42	3.0	66
Accidents (800–999)	9	4.0	225	4.0	225

[a][Confidence limits 95% =] 145–285.
[b][Idem] 123–385.
[c][Idem] 115–877.

V). Surprisingly, overall mortality was significantly increased above expectations, a determining factor being deaths due to cancer and external causes. In particular, 12 malignant cancers were observed against 5.3 expected using the local population for comparison. Hematologic neoplasms (4 observed, 1.1 expected) were significantly increased above what was expected based on local mortality rates. The other cancer sites were stomach (1 case), breast (2), ovary (1), lung (1), rhinopharynx (1), brain (1), and one of unknown primary site. Cardiovascular deaths were clearly lower than expected. The significant increase of accidental deaths was identical whether local or national rates were used to calculate expected deaths.

Analysis by duration of exposure, latency, and year of first exposure did not reveal any definite pattern or trend of mortality for any of the relevant causes. Interpretation, however, is hampered by the limited number of deaths observed. Of

some help, instead, may be a closer look at individual cancer cases (Tables VI, VII). For the six male workers, all hired before 1969, who died of cancer of the digestive tract, the duration of exposure varied between a few months and 22 years and the latency ranged from 5 to 23 years. Two cases of leukemia and one lymphoma were observed, all in subjects hired before 1967, with a variable length of exposure and latency between 2 and 19 years. The three workers who died of lung cancer had also been hired before 1955, but the duration of exposure had been rather short; one lung cancer death was of a clerk hired at an advanced age.

For the four tumors of lymphatic tissue observed in females hired before 1968 (Table VII), the duration of exposure was between 3 months and 33 years, and the latency in one case was only 3 months, in another 2 years, and yet longer in the other two, 15 and 22 years.

DISCUSSION

The small number of deaths limits the interpretation of the results and the conclusions can only be tentative. The cohort of male workers had a limited size and

TABLE VI. Characteristics of Selected Cases of Cancer Deaths Among Male Workers Exposed to PCBs

Cancer type/site (ICD 8th revision)	Age at hire (y)	Year of hire	Length of exposure (y)	Latency (y)	Age at death (y)
Stomach (151)	59	1948	.4	7	66
Stomach (151)	49	1951	17.2	23	72
Liver (155)	33	1957	.3	17	50
Biliary tract (156)	41	1959	1.0	14	55
Pancreas (157)	53	1969	5.8	5	58
Pancreas (157)	35	1960	21.7	22	57
Lung (162)	60	1951	6.7	26	86
Lung (162)	28	1954	.1	7	35
Lung (162)	38	1962	.5	19	57
Reticulum cell sarcoma (200)	27	1952	7.0	15	42
Acute myelocytic leukemia (205)	21	1961	19.0	19	40
Acute hemocytoblastic leukemia (205)	32	1967	2.2	2	34

TABLE VII. Characteristics of Selected Cases of Cancer Deaths Among Female Workers Exposed to PCBs

Cancer type/site (ICD 8th revision)	Age at hire (y)	Year of hire	Length of exposure (y)	Latency (y)	Age at death (y)
Hodgkins disease (201)	20	1960	21.8	22	42
Hodgkins disease (201)	19	1949	12.2	15	34
Hodgkins disease (201)	17	1960	.2	.2	18
Lymphosarcoma (200)	24	1968	.7	2	26

the majority of female workers were still very young. This obviously diminished the chance of observing deaths should exposure have caused harmful effects.

The excessive mortality from malignant cancer among male workers cannot be explained completely by factors not directly addressed by the study, such as, for instance, smoking and other personal habits, socio-economic conditions, place of residence, etc. This can be reasonably derived from two considerations: first, the magnitude of the relative risk noted, varying from 1.8 to 2.5 according to the type of referent mortality considered; second, the evidence of a statistically significant increased risk compared to the local population. In fact, the occupational cohort studied exhibited a pattern of personal/environmental characteristics (education, diet, personal habits, living conditions, etc) quite similar to that of the local population.

Similar considerations apply to the excessive number of deaths from cancer of the digestive system, which were clearly above expectations whether compared with the national or local population. However, interpretation of such a result is limited by an examination of individual cancer cases; of the two workers dying from stomach cancer, one had been hired at an advanced age (which was not unusual in those years) and had experienced a very short exposure, and the other one was a plant guard not involved in production processes; both workers who died from cancer of the liver and biliary tract had been employed in the production area, albeit for rather short periods.The cases of pancreatic cancer occurred in another plant guard (no direct exposure reported) and in a worker who had been exposed directly in the production process for over 20 years. Given this information, no clearcut and definite conclusion regarding the association between cancer of the GI tract and exposure to PCBs can be drawn from the results of the study. There were apparently no grounds for associating lung cancer deaths (although increased above expectations) and exposure in the plant. The numbers were small, the value of the risk estimate was not statistically significant, and such risk had never been suggested before. One case occurred in a manager who started working in the plant at an advanced age in the early years of production, and the other two cases occurred in production workers exposed for very short periods of time. All the three cases of hematologic neoplasms were production workers with a potential for high exposure during the period of their employment (7, 19, and 2 years, respectively). The excess, in comparison with the local population, is high (obs/exp = 2.6); however, it is not statistically significant. Still, the length of the exposures and latency periods make it possible to at least hypothesize an association between working in the plant and a risk of dying from such neoplasms. The worker who died from acute hemocytoblastic leukemia had also had a documented exposure to electromagnetic fields.

Mortality among female workers exhibited some unexpected features. Deaths owing to cardiovascular disease were clearly lower than expected on the basis of the mortality experience of the corresponding general population (both national and local); however, when considering overall mortality, it appeared that some factor(s) had been acting strongly enough to completely neutralize the so-called "healthy worker effect." Factors such as incomplete enumeration of the cohort or errors in the reference mortality rates could be excluded as explanations of the result. In our view, the elevated overall mortality of this group of working females might be explained by differences in social class between the females working in the industry and nonworking females or females not working in the industry, who predominate in the general population. Unlike male workers, however, insufficient information is available for

female workers to allow an understanding of selection phenomena that may differentiate working women in a given geographical area from the remainder of the population of the same sex and age [Gardner, 1986].

It should be further noted that cancer and accidental deaths contributed decisively to this result. As regards accidents, since 7 out of 9 were traffic accidents, one first potential explanation might be social factors differentiating the compared populations, as, for instance, more frequent opportunities for travel and greater use of means of transportation by working as opposed to nonworking females of the same birth cohort. Occupational factors such as work accidents (two electrocutions were noted), also contributed to the observed excess.

The elevated cancer mortality might be interpreted, in our view, in the light of some peculiar occupational factor in addition to the already mentioned social factors. The cancer excess mortality was statistically significant only in comparison with the local population, which, as a matter of fact, was known to have a lower cancer mortality than the national population in the age span relevant to the study. Apart from statistical significance, which can be heavily influenced by the limited number of deaths observed, the suggestion of an increased mortality from all cancer and hematologic neoplasms consistently emerges from the comparison with both reference populations. At least two of the four deaths from lymphatic tumors among women occurred after an exposure and latency period long enough to hypothesize a possible association with the work activity.

Thus, an excessive number of deaths from cancer was observed in both sexes; the sites mainly involved were the lymphatic tissue and the GI tract. These results are fairly consistent with those of experimental studies [Nagasaki et al, 1972; Ito et al, 1973; Kimbrough and Linder, 1974; Kimbrough et al, 1975; National Cancer Institute, 1977; IARC, 1978] and of epidemiological studies carried out after occupational [Brown and Jones, 1982] or accidental [Urabe et al, 1979; Umeda, 1984] exposure.

None of the workers diagnosed as having chloracne in 1954 or 1977 died within the time span of the study. Similarly, all workers whose PCBs blood concentration and skin contamination had been evaluated in 1977 were alive at the end of the follow-up.

In all, five deaths owing to lymphatic tumors were noted. An immunosuppressive action of PCBs on animals had been described [Fishbein, 1974; Allen, 1975], and in 1977, a possible relation between these substances and the onset of lymphomas was suggested [Goldsmith and Guidotti, 1977]. In recent years, the existence of an immunosuppressive effect on humans also was confirmed. In fact, in poisoned subjects, a reduction of immune response, whether humoral or cellular, and a decrease in the T-lymphocytes, mostly of the helper type, has been documented [Chang et al, 1980, 1982a,b; Lu and Wong, 1984]. In our study, the preponderance of forms histologically classified as Hodgkins lymphomas (3 out of 5) renders the hypothesis of an association with PCBs exposure less probable, whether because it is mainly the non-Hodgkin lymphomas that are usually related to industrial carcinogens, or because the Hodgkin lymphoma, during its onset and development, does not seem to be influenced by modifications of the subject's immune response capacity.

Recent investigations [Masuda and Yoshimura, 1984; Kunita et al, 1984; Chen et al, 1984] suggested that polychlorinated quaterphenyls and dibenzofurans, often present as impurities in many PCBs mixtures, are the real causal agents of the toxic effects noted in people exposed to PCBs. These substances, together with dioxins

which may also be present as contaminants, have a toxic action certainly much greater than that of PCBs themselves. Kunita et al [1984], for instance, described a substantial difference in gravity and persistence of toxic effects observed among the Yusho patients and a group of workers intoxicated by PCBs with a very low dibenzofurans contamination. Unfortunately, measurements of possible contaminants of the PCBs mixtures used in the plant studied were not available. Finally, it is worth mentioning that investigations made in different countries [Wright et al, 1982; McDowall, 1983; Milham, 1982; Coleman et al, 1983] pointed out an excess of leukemia deaths among electrical workers that were attributed to exposure to electromagnetic fields. As already mentioned, in the plant studied, there was also a potential for exposure to electromagnetic fields during the testing of large power capacitors.

In summary, results of the present study, admittedly with the limitations already discussed, do nonetheless merge with those coming from previous studies and support the possibility of PCBs posing a carcinogenic risk to humans, at least under the conditions of occupational exposure existing in the past.

The limitations discussed did not permit a causal association to be either proved or dismissed. The follow-up will continue in time. Additional studies, conducted independently in similar settings, will greatly enhance the possibility of verifying the hypothesis of the carcinogenic potential of PCBs suggested by experimental and human studies.

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