

Effects of PCB Exposure on Biochemical and Hematological Findings in Capacitor Workers

by Richard W. Lawton,* Marie R. Ross,† Joseph Feingold‡ and John F. Brown, Jr.*

Certain former operations in capacitor manufacturing resulted in extensive direct contact of the workers with electrical grade polychlorinated biphenyls (PCBs). A study group of 194 such individuals, all exposed to Aroclor 1016 and many previously exposed to Aroclors 1242 and/or 1254, was examined before (1976) and after (1979) discontinuance of PCB use in the operations (1977). At the two examinations, the approximate geometric mean serum levels (in ppb) and 5 to 95% ranges were for lower PCBs (LPCB), 363 (57-2270) and 68 (12-392); and for higher PCBs (HPCB), 30 (6-142) and 19 (4-108), respectively.

The statistical associations among 42 measured clinical chemical and hematological parameters, five different measures of PCB exposure, and seven confounding variables observed in the two examinations were determined by three regression procedures. Similar regressions were performed with DDE, which was present at background levels. The principal statistical findings were a depression in serum bilirubin and elevations in serum GGTP and lymphocyte levels at the time of the first examination, and only an elevation in monocytes at the second. Appraisal of the results suggested an induction of microsomal enzymes which appeared to be subsiding after the cessation of direct exposure to PCBs. The statistical association between serum levels of PCBs and lipids reported by others was confirmed, but shown to be explained by the partitioning behavior of PCB in the body, rather than to changes in liver function. No evidence for health impairment related to PCBs was found, despite the high serum levels of PCBs in the study population.

Introduction

Concern over the human health effects of the polychlorinated biphenyls (PCBs) arises because of the environmental persistence of these substances, which were widely used in the U.S. for nearly 50 years (1929-1978). Several hundred million pounds still remain in existence, either in electrical equipment or in environmental compartments such as landfills, spillage sites or aquatic sediments (1), so that the potential for human exposure continues.

The main growth of PCB usage occurred only after early toxicological studies and extensive industrial experience indicated these materials to be of relatively low toxicity (2-5). In the 1970s, however, PCBs were linked to an outbreak of severe chloracne disease in southwestern Japan in 1968. The outbreak was traced

to the ingestion of rice oil (Yusho) that had been contaminated with thermally decomposed PCB. The toxic agents responsible for "Yusho disease" were ultimately identified as 2,3,4,7,8-pentachlorodibenzofuran and other polychlorinated dibenzofurans (PCDFs) (6), which are formed from PCBs only at very high temperatures (7). Despite contrary evidence, concern has remained that ordinary, unpyrolyzed PCBs, even at residual environmental concentrations, might also produce some human health effects.

In order to identify such effects, a number of epidemiological investigations have been performed on occupationally (8-19) or environmentally (20-22) exposed populations. All such studies have indicated PCB-related health effects in the human to be uncommon, and the only reasonably consistent findings to be statistical associations between the levels of serum PCBs and those of serum lipids, e.g., triglycerides and cholesterol (13,15,21,22). These associations have been interpreted as suggestive of otherwise asymptomatic alterations in liver function.

This interpretation did not recognize that in the body

*General Electric Research and Development Center, P. O. Box 8, Schenectady, NY 12301.

†General Electric Company, Capacitor Products Department, Hudson Falls, NY 12839.

‡Present address: 31 East Street, Fort Edward, NY 12828.

PCBs are partitioned between adipose tissue (the major reservoir) and blood serum in proportion to the lipid content of the serum (23,24). Therefore, statistical associations of serum PCBs with serum lipids and any covariant parameters could arise solely from such partitioning. In order to determine whether PCBs actually do have any effect upon serum lipid levels, it would be necessary to examine the dependence of the latter, not upon the levels of PCB in the serum, but instead upon their levels within the body lipids. For lipid-soluble materials, the concentration within the body's lipid phases has long been recognized as the determinant of the pharmacological response (25).

In addition to the consistently observed association between the levels of PCBs and lipids in the serum, there have been isolated reports of hypertension (22), hepatomegaly (14), chloracne (14,22), other dermal effects (12-14), oxidase induction (16), restrictive lung disease (18), increased levels of serum γ -glutamyl transpeptidase (14,15,22), serum glutamic oxalacetic transaminase (13-15), serum glutamic pyruvic transaminase (12,14), serum ornithin-carbamoyl transferase (14), or serum pseudocholine esterase (14), increased bromsulphthalein retention (12), or reduced plasma HDL cholesterol (15) in the groups studied. Most such reports, however, either lack consistency with the findings of other investigators, or were observed only in groups that were small, lightly exposed to PCBs, and/or exposed to PCBs in combination with other chemicals.

An opportunity to study the effects of unpyrolyzed, electrical grade PCB exposure has been provided at two capacitor manufacturing plants located within a mile of each other along the Hudson River in upstate New York. During their period of PCB use (1946-1977), these plants are believed to have been the largest single U.S. users, consuming about 15% of all U.S. production, and to have had one of the largest PCB-exposed work forces. Between 1946 and 1975, approximately 9500 different employees worked there, and the employment during the 1976-1979 period of this study was between 1500 and 1800.

Previous investigators of this plant population have found its mortality experience (reported as that for "Plant 2" by Brown and Jones) (19) to be normal for all major causes of death, and have indicated a general paucity of significant clinical effects in a volunteer sample drawn from the plant population as a whole (17). However, only 5 to 10% of the plant employees worked in areas or jobs providing direct, continuing exposure to the dielectric fluids. Thus, it appeared probable that this exposed subpopulation, still a sizeable group, might exhibit considerably greater blood PCB levels and physiological effects than the remainder of the plant population.

Accordingly, a study population was selected, using criteria that were broad enough to include the entire directly exposed group, as well as some less directly exposed individuals, and detailed clinical examinations were performed approximately 16 months before and

29 months after the discontinuance of PCB use in the plant. No attempt was made to establish a comparable age- and sex-matched control cohort, but since the study group itself exhibited a distribution of PCB levels covering over two orders of magnitude, analyses within the group offered adequate prospects for identifying and quantifying physiological effects attributable to the PCBs.

Since it was not possible, initially, to decide which of the many clinically measured variables might be affected by PCBs or might confound the study, a three-tiered analysis was used to identify statistically significant associations. In order, these analyses were: (a) a simple linear regression, intrinsically bias-free, for each measured variable or its log transform against each measure of PCB exposure; (b) a multiple linear regression for each of the measured variables against the selected measures of PCB exposure and a series of other independent variables, e.g., sex, age, smoking history, body mass index, etc., believed to have effects on one or more of the clinical variables and (c) a backward stepwise linear regression to remove non significant independent variables. For each regression, statistically significant associations ($p < 0.05$) with the measures of PCB were identified. In addition, the 95% confidence limits of the regression coefficient were used to estimate the significance of the association over the observed range of exposure. Similar regressions were performed for the same measures of p,p' -DDE, which shares with PCBs partitioning behavior in lipids.

Materials and Methods

Description of Environment

In the process used for manufacturing liquid dielectric capacitors, metal foil strips separated by paper layers were wound into tight coils and inserted into metal cans. A cover assembly, having electrical connectors and a port to admit the dielectric fluid, was then sealed to the can. For filling, small capacitors, such as those used in fluorescent light ballasts, were packed onto racks that were placed in large autoclaves, warmed, degassed under vacuum, and then flooded with the dielectric fluid. The racks were then drained, removed, and transported to sealing stations where the port was manually sealed with solder. Large power capacitors were originally filled manually; subsequently, they were filled by an electronically controlled manifold system which reduced spillage and dermal contact. Following sealing, both large and small capacitors were cleaned, degreased, tested, repaired if appropriate, labeled, and packed for shipment. The dielectric fluids were blended with stabilizers, treated with fuller's earth to remove polar impurities, and tested for dielectric properties, thereby producing an "electrical grade" product. The jobs which provided frequent or continuous direct exposure to the dielectric fluids (i.e., direct dermal contact and/or close proximity to a source of vapor) were those associated

with the fluid processing, the handling and sealing of wet capacitors, capacitor salvage and repair, and the quality control laboratory.

Aroclor 1254, a commercial mixture of PCB isomers and homologs having the average molecular composition of a pentachlorobiphenyl, was used initially in the two plants (1946 ff.). During 1953–1955 a transition was made to Aroclor 1242, a PCB mixture having the average composition of a trichlorobiphenyl, for all but a few specialty capacitors. In 1971, all use of Aroclor 1254 was phased out, and Aroclor 1242 was replaced by Aroclor 1016, a PCB mixture that also had the average composition of a trichlorobiphenyl, but which had been redistilled by the manufacturer to remove all homologs containing more than four chlorines per biphenyl. Finally, on June 30, 1977, all PCB use ceased. The stabilizer used with the Aroclor 1254 mixture was β -chloroanthraquinone; that most commonly used with Aroclors 1242 and 1016 was Union Carbide epoxide 4221.

In late 1975, PCB area air levels (reported as Aroclor 1242) around the capacitor filling and sealing area were found to be in the range 200 to 2000 $\mu\text{g}/\text{m}$ (geometric mean, 690 $\mu\text{g}/\text{m}$). Subsequent to the cessation of PCB use they dropped steadily to a mean of 16 $\mu\text{g}/\text{m}$ in April 1983. The TWA levels indicated by personal air samplers on directly exposed personnel in these areas in early 1977 were reported by Brown and Jones (19) to average 168 $\mu\text{g}/\text{m}$ (range, 24–393 $\mu\text{g}/\text{m}$), or about half the mean area levels that we measured at that time. These investigators also measured the levels of trichloroethylene (used in degreasing); tin, lead and zinc (soldering operations); aluminum and iron (welding operations); and toluene and methyl isobutyl ketone (painting operations): all were generally within OSHA standards.

Unfortunately, there are no data regarding PCB air levels during the 1946–1974 period. Major changes in plant ventilation and changes in the Aroclors used made it impossible to estimate those levels.

Study Population

The study population was selected in early 1976 to include all those workers (a) whose jobs required direct occupational contact with PCBs in high air level zones, such as those in handling and sealing wet capacitors, and capacitor salvage and repair; (b) whose jobs did not involve direct PCB contact, but were at the periphery of the high exposure zone; and (c) whose duties required brief high exposure and contact, such as maintenance men. At the time of the 1976 examination, this study population included 152 males and 42 females. Of these, 41 had service times beginning during the period when the predominant dielectric fluid was Aroclor 1254, 103 began service when it was Aroclor 1242, and 50 had been exposed only to Aroclor 1016. The mean service times and ages in the study population were 17 years (range, 2–35) and 40 years (range 20–65), respectively. Thirty-three of the 194 were also members of the 326-

member volunteer group examined by Fischbein et al. a little later in 1976 (17). By the time of our 1979 examination, our directly exposed study group was reduced to 174 workers due to relocation, although still including 14 retired and/or relocated workers who returned for the reexamination.

At the time of the initial population selection an estimate of the relative PCB exposure was made by one of us (M. R.) on the basis of the individual worker's job activities. The estimated exposure categories (abbreviated as EXE below) generally corresponded to those used for selection, e.g., "low" for peripherally exposed jobs; "medium" for those with intermittent exposure; and "high" for those with continuous direct exposure. After the serum PCB data became available, analysis showed that the "low" and "medium" categories were statistically indistinguishable in terms of serum PCB means.

Clinical Measurements

The clinical examinations were conventional but relatively complete. They included a medical history, physical examination by the plant physician (J.F.), ECG, chest X-ray, spirometry, 26-parameter biochemical analysis, hematology, and urinalysis. Body weight was measured in light indoor clothing and height measured without shoes. Systolic and diastolic blood pressure were measured in the seated position to the nearest 5 mm. The participants were instructed to be fasting for the preceding 12-hr period with water *ad libitum*.

The decision to measure serum PCB levels in 1976 was made during the course of the study, so that only 41 workers had the blood samples required for the PCB analysis drawn while fasting; the remainder were recalled and sampled in the nonfasting state. All of the 1979 measurements were made on fasting sera.

In 1979, the physical examination, ECG, and chest X-ray were repeated only in special cases, but the medical history was expanded and improved, particularly in relation to smoking habits. Documentation on alcohol consumption remained incomplete and generally unreliable.

The chest X-rays were read by a local radiologist (R. C. Batt) who coded the findings according to the ILO/UC criteria (CRC/NIOSH (M) 2.8, Rev. 4/80). ECG's were interpreted by one of us (J.F.). Clinical chemical analyses were performed on the serum samples using an SMA-26, and hematological analyses on EDTA venous blood specimens, by Medpath (Teterboro, N.J.). The total serum lipids were measured in 1976 by using the phenol turbidity method, but not in 1979; the method has been criticized (26) as unreliable for total serum lipids. In 1979 serum triglycerides were reported numerically up to 400 mg/dL and thereafter as ≥ 400 mg/dL. WBC differentials were performed manually in 1976 and with the Technicon Hemalog D in 1979. Serum osmolality was calculated from the electrolytes and crystalloids (BUN, blood glucose) by con-

ventional procedures. The mean corpuscular hemoglobin was calculated from the reported red blood cell count and hemoglobin values in 1976.

Serum PCB and DDE Measurements

The PCB determinations upon both the 1976 and 1979 serum samples were performed by Hazelton Raltech (Madison, WI) using conventional PCB extraction, packed column gas chromatographic, and data reporting procedures, which are discussed in detail elsewhere (27). These procedures also provided data on the levels of DDE present. The observed distributions of PCB isomer peaks in the capacitor workers' chromatograms are also described elsewhere (27); they differed markedly from those in the Aroclor 1016, 1242 and 1254 standards because of metabolism and elimination of all of the mono- and dichlorobiphenyl isomers, most of the tri- and tetrachloro, and many of the pentachloro isomers as well.

The serum PCB levels were reported by the analyst in 1976 as levels of Aroclors 1242 and 1254, and in 1979 as Aroclors 1242, 1254, and 1260. These were calculated from the observed chromatograms by ratioing the sums of certain selected peak heights to those of the corresponding peaks in Aroclor standards. The selected peaks were, for Aroclor 1242, those having retention times (relative to that for DDE, times 100) of 37, 70 and 84; for Aroclor 1254, those at 125, 146, 160 and 186; for Aroclor 1260, those at 125, 146, 160, 186, 197, 294 and 372. Because of the differences in PCB composition between the serum samples and the standards, such values overstate the amounts of PCB actually present. The latter are now more commonly described in terms of values for LPCB ("lower PCBs," i.e., all isomers having gas chromatographic retention times on silicone less than that of DDE, which comes in the middle of the pentachlorobiphenyl range), and HPCB ("higher PCBs," i.e., those with retention times > DDE) with the sum of LPCB and HPCB representing the total PCB present (TPCB). We have shown elsewhere (27) that for our more heavily exposed subjects the factor for converting a reported serum Aroclor 1242 value to LPCB is 0.237; for Aroclor 1260 to HPCB, 0.71. The factor for converting the 1976 Aroclor 1254 values to HPCB was estimated from the chromatograms as 0.35.

In 1980 it was found that the individual 1979 values of Aroclor 1242, Aroclor 1254 and DDE, relative to the population means, were highly correlated with the corresponding values in 1976, but that the 1979 values were generally several times higher, despite the limited exposure to either PCB or DDE during the intervening period, indicating that one of the data sets contained a systematic error. Review of the methodology and tests on control samples confirmed the validity of the 1979 procedure (27); however, the standardization error in the 1976 data could not be identified after the 4-year time lapse, and the analyst could not verify the 1976 serum PCB and DDE measurements. Accordingly, we have reported here all such data as the originally reported numerical quantity times a correction factor x .

Determination of the value of x was not required for the statistical association studies, but was for estimates of actual PCB levels and clearance. To estimate x , we used the DDE peak on the chromatograms as an internal standard; there had been no more than background exposure of the study group to this substance, which is highly persistent in the body, during the 1976-1979 period. The geometric mean DDE value for 1979 was calculated directly from the reported data; that for 1976 using the maximum likelihood estimate for censored data (28), since 87 of the 140 1976 values for *p,p'*-DDE had been reported as ≤ 1 ppb. The resulting values (10.2 and 1.18 ppb, respectively) indicated the mean value of x to be about 10, suggesting a possible decimal point error in 1976.

Lipid PCB Determinations

Serum cholesterol lipids (free cholesterol plus cholesterol esters) were estimated from normal values (26) as 1.50 times the clinically reported serum cholesterol (i.e., cholesterol equivalent) values. Total serum neutral lipids were calculated as the sum of the clinically reported serum triglycerides plus the serum cholesterol lipids. Serum lipid PCBs were calculated as the gross serum PCBs divided by serum neutral lipids. It is shown elsewhere (23,24) that PCBs partition between serum and adipose tissue fat in direct proportion to the content of neutral lipids as specified by this procedure; thus, this measure of the serum lipid PCB level is approximately equal to the PCB level in adipose tissue fat. However, the regression results were not particularly sensitive to the exact procedure used for calculating serum lipid phases and comparable findings were obtained when they were calculated instead as simply the sum of the serum triglycerides and the serum cholesterol.

Statistical Analyses

Statistical analyses were performed on a Honeywell 600/6000 computer, using STATPAC (23), a versatile general statistical program with many of the capabilities of the more widely used BMDP series (29), for the distribution plotting; simple, multiple and stepwise linear regression; and maximum likelihood estimates for censored data.

To evaluate the distributions of the dependent variables, probability plots of both the measured and logarithmically transformed data were prepared and compared for linearity. The choice for a number of the distributions seemed equivocal, with the arithmetic and geometric means approximately equal. We generally selected the distributions yielding the highest *F*-ratios in the regressions, or the distributions which tended to produce normal residuals. Partial residual plots were prepared and examined in cases where there was a significant PCB association. Outliers were not removed. The residuals from the regression appeared to be normally distributed with only a few exceptions (blood, glucose, red cell indices), in which cases the distributions were not improved by data transformation.

The independent variables used in the multiple and stepwise regressions, as identified from preliminary studies, were as follows:

- Sex (SEX). Workers were coded as males = 1 and females = 2 so that a positive association represented an attribute of females.
- Age (AGE). The numerical age to the nearest year in 1976 was used. Service time and age covaried ($r = 0.75$).
- Urinary Specific Gravity (SPG). A number of variables appeared sensitive to the degree of hydration in these fasting subjects, principally the crystalloids (blood glucose, blood urea nitrogen).
- Disease Status (DS). Thirteen workers were identified as having significant conditions bearing upon the analysis. They included diabetics (5), those with alcohol problems (3), nonfasting at examination time (3), one worker who was post-pituitary surgery, and one worker with epilepsy taking Dilantin. A dummy variable was created (disease absent = 0, disease present = 1) to identify these cases.
- Nonfasting PCB Measurement (FNF). In the 1976 data individuals whose serum PCB levels were obtained in the nonfasting state were coded as 0; fasting measurements were coded as 1.
- Smoking (SC). Smokers and ex-smokers were coded as 2, nonsmokers as 1.
- Job Status (JS). For the 1979 analysis, workers continuing in employment were coded as 0, separated or retired workers as 1.
- Body Mass Index (BMI). The body mass index (W/H) was calculated for each individual in 1976 and 1979 and used as an independent variable.

In the stepwise regressions, the criterion for adding an independent variable was an F value of 3.0; that for removing a variable was 4.0. The numbers of subjects in the stepwise regressions were only 159–166, rather than the 189–194 used in the simple regressions, because of incomplete data. In addition, 41 cases had missing hematological data in 1976 (Table 1) yielding an N of 128 for these analyses.

Because half of the 1976 gross serum DDE values were reported only as $\leq 1x$ ppb, a dummy variable ($\leq 1x$ ppb = -1, $> 1x$ ppb = +1) was used in the regressions, and no attempt was made to estimate serum lipid DDE values. The 1979 gross serum DDE and serum lipid DDE levels were expressed in the same terms as the corresponding measures of PCB.

Results

Clinical Characteristics of the Study Population

The medical history and physical examination of the study population revealed a variety of clinical conditions and health-related practices.

Sixty-five percent of the population were smokers or ex-smokers, and 26 workers (17%) showed obstructive

patterns on repeated spirometric testing. There were six chest X-ray reports of possible emphysema.

Fifty percent of the population was overweight (>1.2 times the "desirable" weight by 1959 standards (30)) and many were frankly obese. Hypertension histories were obtained on 11.3%. Elevated diastolic pressures (>90 mm Hg) were found in 19.6% of the population at examination in 1976 as compared to 14.7% at the time of employment. Reported urinary tract problems included renal stone or "gravel" in 8 subjects; surgically corrected congenital obstruction in one; bladder, kidney, or prostatic infection in 14; and one benign bladder tumor.

Forty-five workers showed one or more elevated fasting blood glucose values between 1976 and 1979. Of these, 5 were known diabetics, 30 were found to give normal postprandial values, and the remainder showed normal fasting values when retested.

A review of the medical dispensary records of all PCB-exposed employees between 1960 and 1975 revealed 49 visits for contact dermatitis attributed to the dielectric fluid. There were an additional 16 visits for nausea, dizziness, or eye or nasal irritation following short initial exposure to the workplace. In all cases the conditions subsided with removal from exposure. Chloracne was never observed in the plant work force.

Clinical Laboratory Findings

The distributions of clinical chemical and hematological values observed in the study population are described in Table 1, along with the normal ranges unadjusted for sex and age, and asterisks indicating variables having values outside these rough reference ranges.

The numbers of individuals reported by the clinical laboratory to be outside its internal age- and sex-adjusted standards (based on ± 2 standard deviations from mean values) are listed for each reported parameter in Table 2. If the parameters were normal and normally distributed, one would expect four or five cases to fall along each tail of these distributions, making a total of eight to ten.

Table 2 indicated substantial numbers of individuals with elevations in serum triglycerides, cholesterol, and SGPT in both 1976 and 1979, and in blood glucose and albumin/globulin ratio in 1976. Some elevations in BUN and chloride were found in 1979. In 1976 there were some elevations in total WBCs associated with decreased PMNs and increased lymphocytes, monocytes, and eosinophils. In 1979 there were marginal increases in monocytes and eosinophils, but the WBCs were near normal. Urinalysis in both 1976 and 1979 showed elevated cell counts, but no attempt had been made to obtain a clean catch. Urinary specific gravity and calculated serum osmolality were both elevated in 1976 and 1979 (Table 1).

The observed distributions of serum triglycerides and serum cholesterol are shown in greater detail in Figures 1 and 2. The cross-hatched bars represent values that

Table 1. Distribution of clinical laboratory finding in study population of PCB-exposed capacitor workers.

Clinical measurements*	Units	Dist.	Std. range ^b	1976 (N = 194)						1979 (N = 174)					
				Mean	± SD	AM or GM	Percentiles		Missing values	Mean	± SD	AM or GM	Percentiles		Missing values
							5th	95th					5th	95th	
Serum triglycerides	mg/dL	LN	50-200	2.133	0.224	135.8	58.9	310*	1	2.157	0.225	143.7	61.3	336.9*	
Serum total cholesterol	mg/dL	N	125-300	251.3	55.2	251.3	159.2	342.5*	1	238.1	50.1	238.1	155.7	320.4*	
Serum neutral lipids ^c	mg/dL	N		2.709	0.127	512.1	316	829	1	2.702	0.119	503.3	321	789	
SGOT	IU/L	LN	1-50	1.374	0.152	13.3	23.7	41.9		1.448	0.144	28.0	16.3	48.4	2
SGPT	IU/L	LN	1-55	1.460	0.189	28.9	14.1	58.8*	1	1.537	0.164	34.4	18.5	63*	2
SGGTP	IU/L	LN	1-70	1.091	0.266	12.3	4.50	33.8	2	1.198	0.263	15.8	5.82	42.7	
Serum alkaline phosphatase	IU/L	LN	15-55	1.419	0.142	26.2	15.8	43.4		1.465	0.122	29.1	18.4	46.3	
Serum lactic dehydrogenase	IU/L	N	97-250	160.1	28.2	160.1	114.5	205.4		173.6	31.3	173.6	122.1	225.1	
Serum total protein	g/dL	LN	6.2-8.3	0.858	0.079	7.21	6.46	8.04		0.864	0.028	7.30	6.58	8.11	
Serum albumin	g/dL	LN	3.8-5.1	0.648	0.032	4.44	3.92	5.02	1	0.644	0.036	4.41	3.84	5.05	
Serum globulin	g/dL	N	2.1-4.0	2.77	0.51	2.77	1.93	3.60	3	2.92	0.43	2.92	2.21	3.63	
Albumin/globulin ratio		LN	1.2-2	0.213	0.099	1.63	1.12	2.38*	3	0.182	0.082	1.52	1.11	2.07	
Blood urea nitrogen	mg/dL	LN	7-28	1.185	0.119	15.3	9.72	24.0	1	1.227	0.115	16.9	10.9	26.0	
Serum creatinine	mg/dL	N	0.8-1.8	1.30	0.21	1.30	0.95	1.64	1	1.32	0.20	1.32	0.99	1.65	
Bun/creatinine ratio		LN		1.078	0.124	12.0	7.45	19.10	2	1.112	0.127	12.0	8.00	20.9	
Serum total bilirubin	mg/dL	LN	0.1-1.4	-0.339	0.193	0.46	0.22	0.95		-0.218	0.168	0.61	0.32	1.14	
Serum direct bilirubin	mg/dL	N	0-0.4	0.15	0.08	0.15	0.02	0.27	1	0.14	0.07	0.14	0.02	0.26	
Blood glucose	mg/dL	LN	65-130	2.010	0.057	102.4	82.8	126.5	1	1.995	0.056	98.8	79.8	122.3	
Serum uric acid	mg/dL	N	3.3-8.9	5.74	1.25	5.74	3.65	7.80	1	6.01	1.30	6.01	3.88	8.15	
Serum Na	mmole/L	N	134-146	139.5	2.67	139.5	135.1	143.9	2	139.4	2.32	139.4	135.6	143.2	
Serum K	mmole/L	N	3.4-5.4	4.26	0.44	4.26	3.54	4.98	2	4.42	0.46	4.42	3.66	5.17	
Serum Ca	mg/dL	N	8.7-10.5	9.87	0.49	9.87	9.06	10.7*	1	9.67	0.42	9.67	8.97	10.4	
Serum Mg	meq/L	N	1.6-2.3							1.91	0.15	1.91	1.66	2.15	
Serum Cl	mmole/L	N	95-109	102.0	2.93	102.0	97.1	106.8	2	103.8	3.27	103.8	98.4	109.1*	
Serum P	mg/dL	N	1.9-4.3	3.01	0.44	3.01	2.28	3.74	1	2.85	0.44	2.85	2.12	3.58	
Serum osmolality	mosm/kg	N	280-295	299.0	6.06	299.0	288.9	309.0*	2	299.5	5.37	299.5	290.6	304.3*	
Specific gravity (urine)	g/cm ³	N		1.026	0.005	1.026	1.017	1.035*	5	1.026	0.005	1.026	1.018	1.03*	
Serum iron	µg/dL	N	55-200	112.1	36.1	112.1	53.1*	170.6	2	108.2	29.1	108.2	60.3	156.2	
RBC	10 ⁶ /mm ³	N	4.3-6.4	4.94	0.42	4.94	4.24*	5.63	1	5.05	0.39	5.05	4.39	5.70	
HG	g/dL	N	13.0-18.5	14.8	1.67	14.8	12.5*	17.0	1	15.4	1.18	15.4	13.4	17.4	
HCT	%	N	39.5-57.0							46.2	3.55	46.2	40.3	52.1	
MCV	µ ³	N	80-103							91.6	5.18	91.6	83.1	100.0	
MCH ^c	µg	N	26-33	30.0	1.89	30.0	26.9	33.1	1	30.6	1.61	30.6	27.9	33.1	
MCHC	%	N	30.6-36.0							33.5	2.05	33.5	31.2	35.7	
WBC	10 ⁶ /mm ³	N	4.1-11.9	7.02	1.74	7.02	4.21	9.81	2	6.90	1.87	6.90	3.85	9.92	
PMNS	10 ⁶ /mm ³	N	1.65-8.33	4.20	1.32	4.20	2.02	6.37	41	4.12	1.46	4.12	1.77	6.45	
% PMNS	% WBC	N	45-77	59.7	9.57	59.7	44.3	74.9	41	59.0	8.65	59.0	44.6	73.2	
Lymphocytes	10 ⁶ /mm ³	N	1.05-3.58	2.33	0.76	2.33	1.07	3.57	41	2.09	0.64	2.09	1.03	3.14	
% Lymphocytes	% WBC	N	16-45	33.8	9.64	33.8	18.2	49.2*	41	30.9	7.84	30.9	17.9	43.9	
Monocytes	10 ⁶ /mm ³	N	0.06-0.93	0.30	0.17	0.30	0.02	0.59	41	0.48	0.22	0.48	0.12	0.83	
% Monocytes	% WBC	N	0-8	4.38	2.14	4.38	0.87	7.95	41	6.90	2.57	6.90	2.60	11.2*	
Eosinophils	10 ⁶ /mm ³	N	0.04-0.42	0.13	0.13	0.13	0	0.32	41	0.16	0.12	0.16	0	0.33	
% Eosinophils	% WBC	N	0-4	1.84	1.73	1.84	0	4.34*	41	2.34	1.78	2.34	0	4.8*	
Basophils	10 ⁶ /mm ³	N	0.01-0.15							0.046	0.026	0.046	0.003	0.090	
% Basophils	% WBC	N	0-2							0.68	0.38	0.68	0	1.30	

* All blood chemical determinations made on serum; hematology measurements in EDTA venous blood. Abbreviations: SGOT, serum glutamic-oxalacetic transaminase; SGOT, serum glutamic-pyruvic transaminase; SGGTP, serum γ-glutamyl transpeptidase; LDH, serum lactic dehydrogenase; A/G Ratio, albumin/globulin ratio; BUN, blood urea nitrogen; RBC, red blood cell count; HG, hemoglobin; HCT, hematocrit; MCV, mean red cell corpuscular volume; MCH, mean red cell corpuscular hemoglobin; MCHC, mean red cell corpuscular hemoglobin concentration; WBC, white blood cell count; PMN, polymorphonuclear white cells.

^blaboratory standard ranges unadjusted for sex and age. Asterisk (*) indicates values outside these ranges. Arithmetic (AM) or geometric (GM) means given based on selected distribution (N = normal, LN = lognormal).

fell outside the 95th percentile for age from the Lipid Research Clinics Prevalence Study (31). By the LRCPS study criteria, the portions of the male population exhibiting elevations in triglycerides in 1976 and 1979 were 5.7% and 12.6%, respectively. This elevation was significant at the 1% level by paired *t*-test. For females, the elevation in triglycerides was significant at the 5% level but was found in the younger women and appeared to be related in part to obesity and estrogen medication. Of unknown significance were the differences in analytical methodology (fluorimetric method with Techni-

con Autoanalyser used by LRCPS; enzymatic method with discrete analyser used here). The serum cholesterol values (Fig. 2) were normally distributed. By the LRCPS criteria, the portions of the entire group above the 95th percentile in cholesterol in 1976 and 1979 were 29.4% and 23.3%, respectively.

Measures of PCB Exposure

Table 3 shows the means and ranges for serum PCB concentrations described in four ways: first as the Ar-

Table 2. Numbers of study group members reported by clinical laboratory to have clinical variables outside normal (95%) age- and sex-adjusted ranges.

Clinical variables ^a	1976 (N = 194)				1979 (N = 174)			
	Males	Females	Total	+/- Split ^b	Males	Females	Total	+/- Split ^b
Triglycerides	36	4	40	*38/2	38	3	41	*41/0
Total cholesterol	27	7	34	*33/1	20	3	23	*22/1
SGPT	15	0	15	*15/0	12	1	13	*13/0
SGOT	6	1	7	*7/0	3	0	3	3/0
GGTP	6	0	6	*6/0	3	0	3	3/0
Alkaline phosphatase	1	1	2	2/0	5	2	7	4/3
LDH	3	0	3	3/0	2	1	3	3/0
Blood glucose	25	4	29	*29/0	3	3	6	*6/0
Uric acid	2	1	3	2/1	3	0	3	3/0
Total bilirubin	0	0	0	0/0	2	2	4	4/0
Direct bilirubin	1	0	1	1/0	1	1	2	2/0
Total protein	4	0	4	4/0	2	2	4	3/1
Albumin	0	0	0	0/0	8	2	10	1/9*
Globulin	9	3	12	7/7	1	2	3	2/1
A/G ratio	12	2	14	*13/1	6	2	8	4/4
BUN	4	2	6	*6/0	6	3	9	*9/0
Creatinine	1	0	1	1/0	1	0	1	1/0
Na	3	2	5	4/1	2	0	2	0/2
K	3	0	3	1/2	5	1	6	5/1
Cl	1	0	1	0/1	9	4	13	*11/2
Ca	1	1	2	0/2	3	2	5	3/2
P	0	0	0	0/0	1	0	1	0/1
Mg					1	0	1	0/1
Iron	5	1	6	5/1	6	0	6	2/4
RBC	2	1	3	1/2	1	0	1	0/1
Hemoglobin	3	0	3	3/0	2	0	2	1/1
Hematocrit	1	0	1	1/0	4	0	4	5/1
MCV					4	0	4	3/1
MCH					10	1	11	*8/3
MCHC					1	0	1	0/1
WBC	11	2	13	9/4	8	3	11	7/4
Differential								
PMNs	7	4	11	2/9*	1	0	1	1/0
Lymphocytes	8	5	13	*11/2	8	2	10	5/5
Monocytes	7	2	9	*9/0	3	3	6	*6/0
Eosinophils	6	1	7	*7/0	4	2	6	*6/0
Basophils								
Urinalysis								
Albumin	3	2	5	5/0	0	1	1	1/0
Acetone	1	1	2	2/0	2	1	3	3/0
Cells	12	12	24	*24/0	4	8	12	*12/0

^aSee Table 1 for abbreviations used.^bAsterisk (*) indicates significant probability (95%) of increase or decrease assuming a true binomial proportion of 0.5.

oclor levels reported by the analytical laboratory, based on measurements of selected peak heights; second, as LPCB or HPCB values, representing total PCBs actually present in the specified ranges, determined by applying appropriate conversion factors to each reported Aroclor value (27); third, as total PCBs (TPCB), the sum of the LPCB and HPCB values obtained from the Aroclor 1242 and 1260 values, respectively; and fourth, as serum lipid PCB values, obtained by dividing the serum LPCB, HPCB, or TPCB values by the total serum neutral lipid. Also shown are the corresponding data for *p,p'*-DDE, which was present at background levels.

Reference values were obtained on 25 office workers in a Connecticut office in 1979. Their geometric mean analytical values were for serum Aroclor 1242, 6.6 ppb;

for Aroclor 1254, 14.4 ppb; for Aroclor 1260, 8.3 ppb; for *p,p'*-DDE, 11.3 ppb. Thus, taking the correction factor *x* for the 1976 data as 10, the mean xenobiotic levels in the study population in 1976 and 1979 were, for Aroclor 1242, about 220 and 40 times the background levels, respectively; for Aroclor 1254 and 1260, about 4–6 times the background; and for DDE, about the same as background.

Also for *x* = 10, Table 3 indicates that in the 44 to 45 months between the 1976 and 1979 examinations, the geometric mean level of serum Aroclor 1242 fell from 1470 to 277 ppb, or 81%, and that of serum Aroclor 1254 from 84 to 55 ppb, or 35%. Both calculations must be taken with caution, given the imprecision of the analysis, since they are uncorrected for changes in the composition of the study population and highly depen-

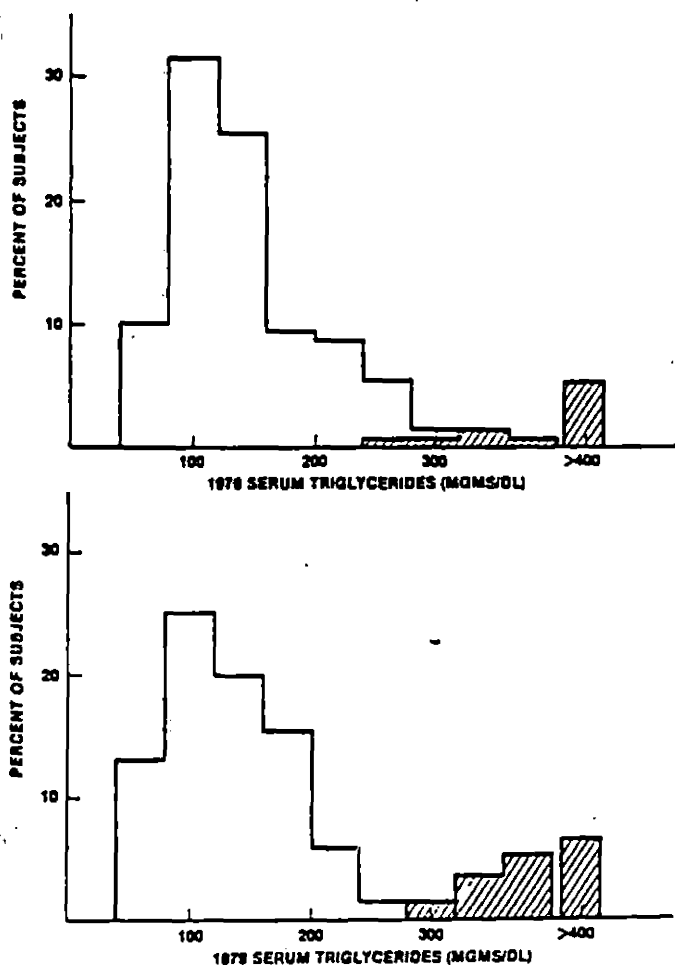


FIGURE 1. Serum triglyceride levels (mg/dL) in the study population. Cross-hatched area indicates values falling above the 95th percentile for age from the Lipid Research Clinics Prevalence Study (31).

dent upon the estimated value of the correction factor, α . The implied extent of clearance of retained LPCB is less sensitive to the estimated value of α , but more difficult to interpret, since some direct exposure to Aroclor 1016 continued during the first third of the interval between the examinations. Investigation of the rates of clearance of individual PCB isomers in this population is continuing.

Because of the analytical uncertainties in the 1976 serum PCB data, we also examined two other measures of PCB exposure, namely, the estimates of relative exposure based on analysis of the individual job activities, and the measurements of PCB air levels in the various working areas, made at the time of the 1976 examination. The correlations of these measures with the 1976 and 1979 serum LPCB and HPCB values are shown in Table 4.

The measurements of area air levels proved to be a poor estimate of exposure, and were dropped from further consideration in the regressions against clinical variables. The relative exposure estimate showed a high correlation with serum LPCB in 1976 ($r = 0.73$, declining to 0.51 in 1979), indicating that it reflected estimated current exposure to Aroclor 1016, which was

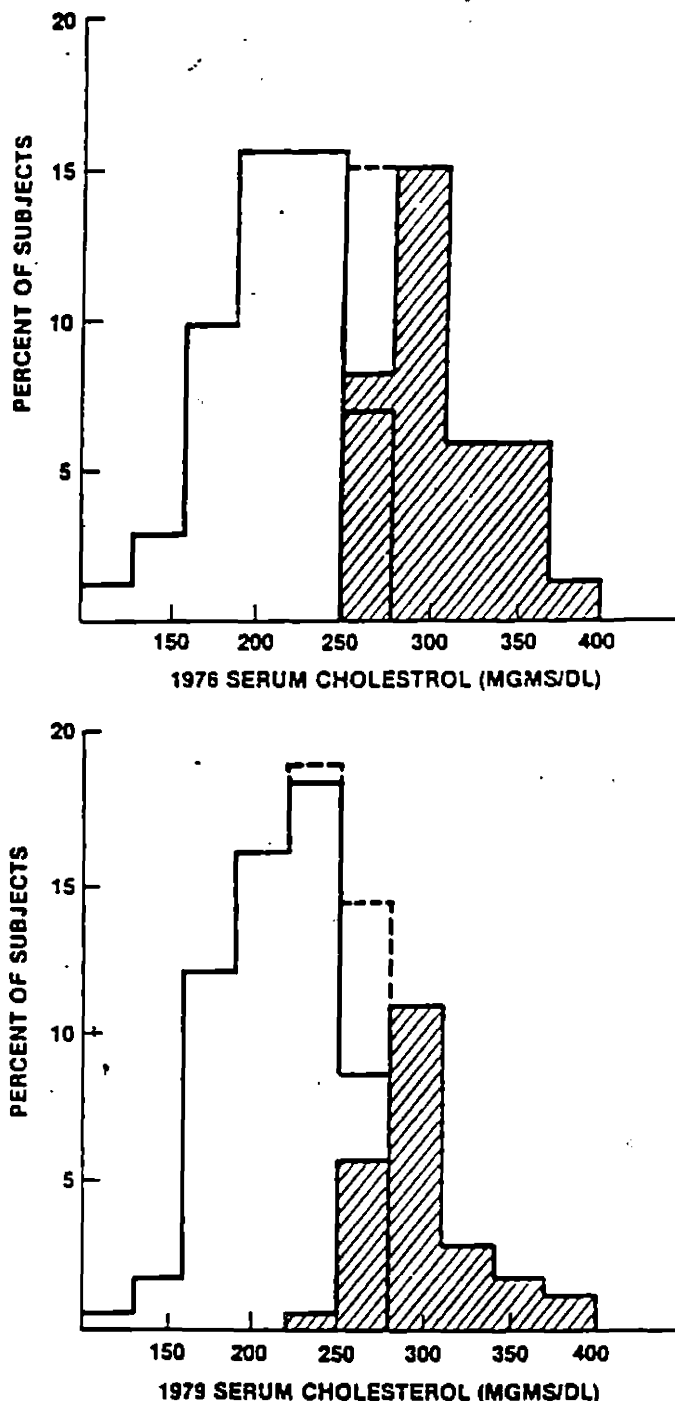


FIGURE 2. Serum total cholesterol levels (mg/dL) in the study population. Cross-hatched areas indicate values falling above the 95th percentile for age from the Lipid Research Clinics Prevalence Study (31).

in use at the time. The correlations between the exposure estimate and the serum HPCBs were lower but equal in 1976 and 1979 ($r = 0.36$).

Relationships of Independent Variables to PCB Exposure

The correlation coefficients for the association of the individual independent variables selected for the re

Table 3. Distributions of serum PCB and DDE in study population of PCB-exposed capacitor workers.

Descriptor of serum parameter	1976						1979					
	log mean	± SD	GM ^b	Percentiles		MV ^c	log mean	± SD	GM ^c	Percentiles		MV ^c
	- log σ^a			5	95		5			95		
Measures of lower PCBs												
Aroclor 1242, ppb	2.167	0.486	147.1x	23.4x	926.2x	9	2.443	0.463	277.1	48.1	1598.1	1
LPCB, ppb	1.560	0.481	36.3x	5.7x	226.9x	9	1.832	0.463	67.9	11.8	391.6	1
Lipid LPCB, ppm	0.968	0.474	9.3x	1.5x	56.3x	9	1.245	0.432	17.6	3.4	90.3	1
Measures of higher PCBs												
Aroclor 1254, ppb	0.924	0.414	8.4x	1.8x	40.3x	9	1.740	0.442	54.9	10.3	292.4	1
Aroclor 1260, ppb							1.543	0.447	34.9	6.4	190.0	30
HPCB (1254), ppb	0.472	0.411	3.0x	0.6x	14.2x	9	1.285	0.442	19.3	3.6	107.7	1
HPCB (1260), ppb							1.375	0.447	23.7	4.4	129.2	30
Lipid HPCB (1254), ppm	- 0.120	0.396	0.8x	0.2x	3.4x	9	0.695	0.400	5.0	1.1	22.7	1
Lipid HPCB (1260), ppm							0.785	0.406	6.1	1.3	28.6	30
Measures of total PCBs												
TPCB (1242, 1260), ppb							1.979	0.437	95.2	18.2	499.0	30
Lipid TPCB, ppm							1.392	0.405	24.6	5.3	114.4	30
Measures of p,p'-DDE												
DDE, ppb	0.033		1.08x			27	1.005	0.318	10.1	3.0	33.7	1
Lipid DDE, ppm							0.305	0.284	2.0	0.7	6.0	1

^a GM = geometric mean; MV = missing values.

^b Most likely value of $\log \alpha = 1.0$; $\alpha = 10$.

Table 4. Correlation coefficients for associations between serum PCB levels, area air levels, and the job analysis exposure estimate in 1976 and 1979.

	1976		1979	
	Exposure estimate (N = 181)	Area air level (N = 180)	Exposure estimate (N = 172)	Area air level (N = 100)
LPCBs (1242)				
Gross serum concn.	0.731	0.144	0.506	-0.014
Serum lipid concn.	0.727	0.167	0.516	0.029
HPCBs (1254)				
Gross serum concn.	0.368	0.080	0.360	-0.029
Serum lipid concn.	0.360	0.102	0.369	0.010
HPCBs (1260)				
Gross serum concn.			0.359	-0.025
Serum lipid concn.			0.363	0.014
Exposure estimate	1.0	-0.084	1.0	-0.164

gression study with the various measures of PCB exposure, as obtained by simple regression, are shown in Table 5.

The tabulated data indicated strong associations of age and/or service time with HPCBs in both 1976 and 1979, and with LPCBs in 1979, probably reflecting a time-dependent accumulation of the more slowly metabolized PCB isomers. There were significant negative correlations between the body mass index and the serum lipid LPCB in 1976 and significant positive correlations with the gross serum LPCBs and HPCBs in 1979. In 1979, LPCB values were significantly higher in females than males (positive sign of coefficient) but lower in smokers (negative sign), probably reflecting oxidase induction (32). 1979 PCB levels in retirees were not significantly different from those in workers who continued in employment. Urinary specific gravity (SPG) and the presence of diabetes or alcoholism showed no association

with serum PCB levels, but SPG was the one independent variable showing association with the exposure estimate in 1976. Higher levels of LPCBs were found in nonfasting individuals in 1976.

Relationships of Clinical Laboratory Findings to PCB Exposure

Tables 6, 7, 8 and 9 show the results of applying the three regression procedures to the clinical laboratory findings using as independent variables the 1976 and 1979 levels of LPCB, HPCB, and DDE (each expressed as both the log gross serum and log serum lipid value except for DDE in 1976), and the PCB exposure estimate (EXE), respectively. In each case, we have tabulated the regression coefficients for the associations with PCB or DDE, β_1 , and their confidence intervals for those clinical parameters that showed a significant

Table 5. Correlation coefficients relating measures of PCB exposure and the selected independent variables.

Dependent variable	Independent variables								
	Age	Ser	Sex	SPG	BMI	DS	SC	FNF	JS
Gross serum PCBs									
LPCBs, 1976	0.107	0.073	0.011	-0.121	-0.090	-0.045	-0.132	-0.188*	
LPCBs, 1979	0.259*	0.191*	0.160*	0.084	0.208*	0.096	-0.173*		-0.015
HPCBs, 1976	0.421*	0.394*	-0.091	-0.111	-0.013	-0.086	0.009	-0.021	
HPCBs, 1979	0.516*	0.549*	-0.026	0.037	0.189*	0.141	-0.050		0.005
Serum lipid PCBs									
LPCBs, 1976	0.028	-0.007	0.030	-0.111	-0.172*	-0.121	-0.172*	-0.211*	
LPCBs, 1979	0.209*	0.140	0.185*	0.077	0.136	0.061	-0.199*		-0.008
HPCBs, 1976	0.340*	0.314*	-0.014	-0.099	-0.109	-0.001	-0.037	-0.045	
HPCBs, 1979	0.493*	0.535*	0.014	0.026	0.114	0.109	-0.069		0.014
Exposure estimate									
1976	0.004	-0.009	-0.040	-0.158*	-0.106	-0.115	-0.109	-0.138	
1979	0.004	-0.009	-0.040	-0.062	-0.036	-0.115	-0.109		0.084

*Statistical significance $\leq 5\%$.

Table 6A. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum LPCB, as determined by three regression procedures: log gross serum LPCBs.

Log gross serum LPCBs ^b										
Dependent variable ^a	r	Simple regression			Multiple regression			Step regression		
		$\hat{\beta}_1$	Confid. limits		$\hat{\beta}_1$	Confid. limits		$\hat{\beta}_1$	Confid. limits	
			5	95		5	95		5	95
1976										
Log triglycerides	2.14	0.07	0.01	0.14	0.10*	0.03	0.17	0.10*	0.03	0.16
Cholesterol	252	24.9*	8.48	41.4	24.3*	7.15	41.5	25.7*	9.49	42.0
Log SGPT	1.46	0.03	-0.01	0.09	0.07*	0.02	0.13	0.08*	0.02	0.13
Log GGTP	1.10	0.07	-0.01	0.15	0.12*	0.04	0.21	0.13*	0.05	0.21
Log total bilirubin	-0.34	-0.09*	-0.14	-0.03	-0.08*	-0.15	-0.02	-0.09*	-0.15	-0.03
Direct bilirubin	0.15	-0.03*	-0.06	-0.01	-0.04*	-0.06	-0.01	-0.04*	-0.06	-0.01
Uric acid	5.73	0.08	-0.31	0.46	0.31	-0.01	0.64	0.35*	0.04	0.66
Log blood glucose	2.01	-0.01	-0.03	0.01	-0.001	-0.02	0.02	-0.001	-0.02	0.01
Phosphorus	3.01	0.14*	0.01	0.27	0.20*	0.04	0.35	0.16*	0.01	0.30
RBC	4.94	-0.07	-0.20	0.06	-0.07	-0.18	0.05	-0.08	-0.19	0.02
Lymphocytes	2.33	0.03*	0.04	0.55	0.42*	0.12	0.71	0.35*	0.07	0.63
1979										
Log triglycerides	2.16	0.18*	0.11	0.25	0.15*	0.08	0.22	0.14*	0.07	0.21
Cholesterol	238	34.3*	18.8	49.8	25.6*	8.81	42.4	24.0*	7.90	40.1
Log GGTP	1.20	0.11*	0.03	0.20	0.10*	0.02	0.19	0.12*	0.04	0.20
Log total protein	0.86	0.01*	0.002	0.02	0.01	-0.001	0.02	0.01	-0.001	0.02
Globulin	2.92	0.19*	0.05	0.33	0.10	-0.05	0.24	0.13	-0.005	0.25
Hemoglobin	15.4	-0.04*	-0.78	-0.02	-0.20	-0.56	0.16	-0.20	-0.54	0.13
% Lymphocytes	30.9	-0.49	-3.02	2.04	-1.92	-4.69	0.85	-1.44	-4.31	1.00
Monocytes	0.48	0.07*	0.01	0.14	0.09*	0.02	0.17	0.08*	0.01	0.15
% Monocytes	6.96	1.18*	0.38	1.99	1.41*	0.54	2.27	1.41*	0.58	2.23

^aSee Table 1 for abbreviations. Asterisk (*) indicates 95% confidence limits did not include zero.^bN (1976) for simple regression = 189-194. N for multiple regression and step regression = 159-166 except hematology where there are 41 missing values (Table 1).

association in one of the six regressions performed. The test of significance was that the 95% confidence interval for β_1 not include zero; statistically significant associations are indicated by asterisks. In addition, in Tables 6-8 we have listed the partial r values for the backward step regressions against the log serum lipid xenobiotic (e.g., LPCB, HPCB or DDE) and the other independent variables. The partial r values listed are generally those

where the regression coefficient was found to be of statistical significance, which, depending on the number of degrees of freedom, generally corresponded to a partial $r > 0.15$; in addition, we have listed some borderline associations, as indicated by partial r values of 0.14-0.15. A comparison of the β_1 values across these various regressions indicates the sensitivity of the relation to confounding by the other independent variables, and

Table 6B. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum LPCB, as determined by three regression procedures log serum lipid LPCBs.

Dependent variable*	Log serum lipid LPCBs*								
	Simple regression			Multiple regression			Step regression		
	β_1	Confid. limits		β_1	Confid. limits		β_1	Confid. limits	
		5	95		5	95		5	95
1976									
Log triglycerides	-0.04	-0.11	0.03	0.01	-0.07	0.08	0.01	-0.07	0.08
Cholesterol	-1.65	-18.8	15.5	1.82	-16.4	20.1	-1.82	-16.4	20.1
Log SGPT	-0.002	-0.06	0.06	0.05	-0.01	0.11	0.05	-0.01	0.10
Log GGTP	0.02	-0.06	0.10	0.10*	0.01	0.19	0.11*	0.02	0.19
Log total bilirubin	-0.08*	-0.04	-0.02	-0.09*	-0.15	-0.02	-0.09*	-0.15	-0.03
Direct bilirubin	-0.03*	-0.05	-0.01	-0.04*	-0.06	-0.01	-0.04*	-0.06	-0.01
Uric acid	-0.09	-0.48	0.30	0.25	-0.09	0.59	0.31	-0.02	0.63
Log blood glucose	-0.02*	-0.04	-0.003	-0.003	-0.02	0.01	-0.003	-0.02	0.01
Phosphorus	0.16*	0.02	0.29	0.22*	0.06	0.38	0.19*	0.04	0.34
RBC	-0.01	-0.23	0.03	-0.11	-0.23	0.01	-0.12*	-0.23	-0.01
Lymphocytes	0.23*	0.01	0.54	0.38*	0.08	0.69	0.39*	0.09	0.69
1979									
Log triglycerides	0.08	-0.01	0.16	0.05	-0.03	0.13	0.04	-0.03	0.12
Cholesterol	12.2	-5.20	29.6	2.64	-15.5	20.8	2.88	-14.7	20.4
Log GGTP	0.07	-0.02	0.16	0.07	-0.02	0.16	0.07	-0.02	0.16
Log total protein	0.007	-0.003	0.02	0.003	-0.01	0.01	0.003	-0.01	0.01
Globulin	0.12	-0.26	0.27	0.02	-0.13	0.17	0.02	-0.13	0.17
Hemoglobin	-0.59*	-1.00	-0.19	-0.31	-0.69	0.06	-0.32	-0.68	0.03
% Lymphocytes	-1.67	-4.38	1.03	-3.25*	-6.14	-0.39	-1.95	-4.65	0.75
Monocytes	0.08*	0.01	0.16	0.11*	0.03	0.19	0.10*	0.02	0.17
% Monocytes	1.36*	0.50	2.21	1.61*	0.71	2.52	1.58*	0.71	2.46

* N (1979) for simple regression = 172-174. N for multiple regression and step regression = 165-166.

Table 6C. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum LPCB, as determined by three regression procedures independent variables.

Dependent variable*	Independent variables*										
	Step regression			Partial r							
	β_1	Confid. limits		Age	Sex	SPG	BMI	DS	SC	JS	Log (LPCB) _{SL}
		5	95								
1976											
Log triglycerides	0.01	-0.07	0.08	0.20	-0.22	-0.15	0.23	0.26		X	
Cholesterol	1.82	-16.4	20.1	0.35			0.20			X	
Log SGPT	0.05	-0.01	0.10		-0.29		0.35			X	
Log GGTP	0.11*	0.02	0.19		-0.19		0.15			X	0.29
Log total bilirubin	-0.09*	-0.15	-0.03			0.20		0.15		X	-0.22
Direct bilirubin	-0.04*	-0.06	-0.01		-0.17			-0.19	-0.20	X	-0.21
Uric acid	0.31	-0.02	0.63	-0.47			0.45			X	0.16
Log blood glucose	-0.003	-0.02	0.01	0.14			0.32	0.39		X	0.19
Phosphorus	0.19*	0.04	0.34						0.16	X	0.19
RBC	-0.12*	-0.23	-0.01		-0.58					X	-0.17
Lymphocytes	0.39*	0.09	0.69							X	0.16
1979											
Log triglycerides	0.04	-0.03	0.12	0.19			0.40				X
Cholesterol	2.88	-14.7	20.4	0.34			0.18				X
Log GGTP	0.07	-0.02	0.16	0.16	-0.26	0.18	0.21				X
Log total protein	0.003	-0.01	0.01	-0.14			0.23		0.19		X
Globulin	0.02	-0.13	0.17				0.27			-0.15	X
Hemoglobin	-0.32	-0.68	0.03		-0.54						X
% Lymphocytes	-1.95	-4.65	0.75							0.19	
Monocytes	0.10*	0.02	0.17						0.21	-0.21	X
% Monocytes	1.58*	0.71	2.46		-0.16		-0.15			-0.23	X

* See text for abbreviations.

Table 7A. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum HPCB (1254), as determined by three regression procedures: log gross serum HPCBs^ac

Log gross serum HPCBs										
Dependent variable ^a	$\bar{x}$	Simple regression			Multiple regression			Step regression		
		β_1	Confid. limits		β_1	Confid. limits		β_1	Confid. limits	
			5	95		5	95		5	95
1976										
Log triglycerides	2.14	0.13*	0.06	0.21	0.11*	0.01	0.20	0.12*	0.04	0.21
Cholesterol	251.9	38.7*	19.8	57.6	31.1*	7.63	54.6	35.1*	13.1	57.1
Log SGPT	1.46	0.04	-0.03	0.11	0.08*	0.002	0.15	0.06	-0.003	0.13
Log GGTP	1.10	0.12*	0.03	0.21	0.15*	0.03	0.26	0.15*	0.05	0.25
Log alk. phos.	1.42	0.07*	0.02	0.11	0.06	-0.004	0.13	0.07*	0.01	0.12
Log total bilirubin	-0.34	-0.08*	-0.15	-0.02	-0.12*	-0.21	-0.03	-0.10*	-0.18	-0.03
Direct bilirubin	0.15	-0.03	-0.05	0.001	-0.04*	-0.08	-0.006	-0.04*	-0.07	-0.008
Log total protein	0.86	-0.002	-0.01	0.01	-0.01	-0.02	0.01	-0.006	-0.02	0.01
Log albumin	0.65	-0.01	-0.02	0.003	-0.008	-0.02	0.007	-0.007	-0.02	0.008
Log BUN	1.19	0.04*	0.001	0.09	0.02	-0.04	0.06	0.02	-0.03	0.06
Creatinine	1.30	-0.01	-0.09	0.06	-0.06	-0.15	0.03	-0.05	-0.13	0.04
Log B/C ratio	1.08	0.05*	0.002	0.09	0.04	-0.02	0.09	0.04	-0.01	0.08
Iron	110.7	-13.6*	-26.1	-1.16	-10.5	-27.3	6.33	-10.1	-24.1	4.14
RBC	4.94	-0.08	-0.23	0.07	-0.06	-0.21	0.10	-0.09	-0.22	0.04
WBC	7.0	1.00*	0.40	1.59	1.34*	0.55	2.14	0.95*	0.28	1.63
Lymphocytes	2.33	0.23*	0.02	0.63	0.72*	0.29	1.15	0.70*	0.27	1.13
% Monocytes	4.37	-1.07*	-1.91	-0.23	-1.03*	-2.98	-0.63	-1.67	-2.61	-0.73
1979										
Log triglycerides	2.16	0.22*	0.15	0.29	0.19*	0.10	0.27	0.19*	0.12	0.26
Cholesterol	238.2	47.3*	31.6	63.0	36.1*	15.9	56.3	39.4*	20.7	58.2
Log GGTP	1.20	0.14*	0.05	0.22	0.07	-0.03	0.17	0.10*	0.02	0.19
Log alk. phos.	1.47	0.06*	0.02	0.10	0.04	-0.01	0.10	0.05*	0.01	0.10
Direct bilirubin	0.14	-0.02	-0.05	0.004	-0.02	-0.05	0.01	-0.02	-0.05	0.001
Log blood glucose	2.00	0.04	-0.02	0.06	0.02	-0.003	0.04	0.02*	0.003	0.04
Globulin	2.92	0.21*	0.07	0.36	0.11	-0.07	0.29	0.12	-0.02	0.27
Log A/G ratio	0.18	-0.04*	-0.06	-0.01	-0.01	-0.04	0.02	-0.01	-0.04	0.02
Log BUN	1.23	0.08*	0.04	0.12	0.04	-0.001	0.09	0.05*	0.005	0.09
Log B/C ratio	1.11	0.06*	0.02	0.11	0.03	-0.02	0.09	0.04	-0.01	0.09
Monocytes	0.48	0.08*	0.01	0.16	0.10*	0.01	0.19	0.08*	0.01	0.16
% Monocytes	6.96	1.23*	0.38	2.07	1.32*	0.25	2.38	1.13*	0.27	1.99

^aSee Table 6 footnotes.

the effects of conversion from gross serum to serum lipid concentration of the xenobiotic.

The most consistent finding in Tables 6-9 was the strong, positive associations of log serum triglycerides and cholesterol with the log gross serum level of PCBs and DDE which has been found by others (13,15,21,22). The association disappeared when the xenobiotic level was expressed as the concentration in serum lipids, or as the PCB exposure estimate. This disappearance was associated with a 70 to 130% decline in the value of β_1 . This finding was exhibited in all regressions whether against log LPCB, HPCB, or DDE, and whether for 1976 or 1979. A similar, but less dramatic change was exhibited by regressions against measures of the hepatic enzymes (log GGTP, log SGPT and log alkaline phos phatase). These parameters frequently showed significant associations with the log gross serum levels of PCB or DDE, but the β_1 values dropped 20 to 50% upon conversion to serum lipid levels. The only associations then remaining significant in the final backward regressions were those of 1976 log GGTP with log PCB, log HPCB, and EXE. None of the other clinical

parameters showed consistent declines of this magnitude in β_1 .

A second consistent finding was strong negative associations of PCBs, but not DDE, with the two measures of bilirubin, direct bilirubin and log total bilirubin, in 1976. These associations were seen for all measures of log PCB (LPCB, HPCB and EXE) in almost all of the regressions. Only two associations remained in 1979 (HPCB, EXE), when the PCB levels were lower.

A third set of findings consisted of associations between the hematological variables and the serum lipid PCBs. In 1976 significant negative associations were found between RBCs and both log serum lipid LPCB and HPCB, and between the monocytes and both log serum lipid HPCB and the exposure estimate. There were positive associations between lymphocytes and log serum lipid LPCB, and between WBCs and log serum lipid HPCB. Similar associations with the log gross serum DDE were found for the lymphocytes, monocytes, and WBCs. In separate step regression studies log total bilirubin was selected in place of log serum lipid PCB values in the cases of RBCs and the lympho-

Table 7B. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum HPCB (1254), as determined by three regression procedures: log serum lipid HPCBs.

Dependent variable*	Log serum lipid HPCBs								
	Simple regression			Multiple regression			Step regression		
	β_1	Confid. limits		β_1	Confid. limits		β_1	Confid. limits	
		5	95		5	95		5	95
1976									
Log triglycerides	-0.02	-0.10	0.06	-0.07	-0.17	0.03	-0.08	-0.17	0.02
Cholesterol	2.68	-17.8	23.2	-11.1	-35.3	13.1	-11.5	-35.6	12.6
Log SGPT	-0.01	-0.08	0.06	0.03	-0.04	0.11	0.03	-0.04	0.10
Log GGTP	0.06	-0.04	0.16	0.09	-0.02	0.21	0.11*	0.002	0.21
Log alk. phos.	0.04	-0.02	0.09	0.02	-0.04	0.09	0.03	-0.03	0.09
Log total bilirubin	-0.08*	-0.15	-0.01	-0.12*	-0.21	-0.03	-0.11*	-0.19	-0.02
Direct bilirubin	-0.02	-0.05	0.005	-0.04*	-0.07	-0.001	-0.03*	-0.07	-0.002
Log total protein	-0.005	-0.02	0.01	-0.01	-0.03	0.01	-0.015*	-0.03	-0.003
Log albumin	-0.01	-0.02	0.002	-0.01	-0.03	0.002	-0.014*	-0.028	-0.001
Log BUN	0.03	-0.01	0.07	0.003	-0.05	0.05	0.003	-0.05	0.05
Creatinine	-0.05	-0.1	0.03	-0.10*	-0.18	-0.01	-0.09*	-0.18	-0.01
Log B/C ratio	0.05*	0.002	0.09	0.04	-0.02	0.09	0.04	-0.01	0.09
Iron	-15.2*	-28.1	-2.21	-13.1	-29.9	3.77	-13.2	-28.2	1.74
RBC	-0.13	-0.28	0.03	-0.12	-0.28	0.03	-0.15*	-0.29	-0.02
WBC	0.97*	0.35	1.59	1.20*	0.39	2.01	0.98*	0.26	1.69
Lymphocytes	0.30	-0.02	0.62	0.58*	0.14	1.02	0.36	-0.02	0.74
% Monocytes	-0.87	-1.77	0.02	-1.45*	-2.64	-0.60	-1.61*	-2.63	-0.59
1979									
Log triglycerides	0.11*	0.03	0.20	0.04	-0.06	0.13	0.04	-0.06	0.13
Cholesterol	25.3*	6.72	43.9	2.06	-20.1	24.2	2.19	-19.6	24.0
Log GGTP	0.09	-0.01	0.19	0.02	-0.09	0.13	0.02	-0.09	0.13
Log alk. phos.	0.05*	0.003	0.10	0.03	-0.03	0.08	0.03	-0.01	0.08
Direct bilirubin	-0.02	-0.05	0.004	-0.02	-0.06	0.01	-0.03*	-0.06	-0.002
Log blood glucose	0.04*	0.02	0.06	0.02	-0.01	0.04	0.02	-0.005	0.04
Globulin	0.14	-0.02	0.31	-0.004	-0.19	0.18	-0.004	-0.19	0.18
Log A/G ratio	-0.02	-0.04	0.01	0.001	-0.03	0.04	0.001	-0.03	0.04
Log BUN	0.08*	0.03	0.12	0.04	-0.01	0.08	0.04	-0.003	0.09
Log B/C ratio	0.05*	0.01	0.10	0.02	-0.03	0.08	0.02	-0.03	0.08
Monocytes	0.10*	0.03	0.18	0.12*	0.03	0.22	0.11*	0.03	0.19
% Monocytes	1.48*	0.55	2.41	1.56*	0.44	2.69	1.42*	0.48	2.36

*See Table 6 footnotes.

cytes. Similar selections, reflecting similar co linearities, occurred in the cases of phosphate (with LPCB) and creatinine (with HPCB). Smoking was a significant confounding variable in the cases of direct bilirubin, WBCs, and phosphate.

In 1979 strong positive associations were found between all measures of exposure to PCB (but not DDE) and the absolute and relative monocyte levels. The bilirubins did not replace PCBs in the step regressions, but smoking was a significant confounder. The positive associations of cholesterol and serum sodium with the relative exposure estimate in 1976 and the negative association of log serum lipid DDE with serum iron in 1979 appeared to be singular findings.

The 1530 regressions used to generate the data shown in Tables 6-9 showed at least one significant association (5% level) with one measure of exposure in one of the regressions for 26 of the 42 clinical variables. The incidence of significant associations with the clinical variables was positively influenced by the number of independent variables included in the regressions. The independent variables used in Tables 6-9 regressions

all showed multiple associations with the clinical laboratory parameters. This group of independent variables did not, however, include measures of alcohol consumption or socioeconomic status, both of which have been used in other studies (21,22). The data available indicates that there can be important colinearities among the dependent variables. Because of the uncertainties presented by chance associations, unused or unidentified confounders, and colinearities among variables we have focussed our interpretations upon those associations that were seen consistently in the step regressions against log serum lipid PCBs, but not in the corresponding regressions against log DDE.

The mean β_1 coefficients of Tables 6-9 express the best estimates of the dependence of the clinical laboratory variables on log PCB, and their 95% confidence limits indicate the uncertainties of these estimates. For associations observed to be statistically significant we have multiplied the lower and upper β_1 confidence limit values by the observed range of log PCBs in order to determine whether the product resulted in values for the laboratory variables outside the normal expected

Table 7C. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum HPCB (1254), as determined by three regression procedures: independent variables.

Dependent variable	Independent variables ^a								
	Partial r								
	Age	Sex	SPG	BMI	DS	SC	JS	FNF	Log (HPCB) _{SL}
1976									
Log triglycerides	0.20	-0.22	-0.15	0.28	0.26		X		
Cholesterol	0.35			0.20			X		
Log SGPT		-0.29		0.37			X		
Log GGTP		-0.18		0.19			X	0.28	0.16
Log alk. phos.					0.14		X		
Log total bilirubin			0.21		-0.17		X	0.15	-0.20
Direct bilirubin		-0.17				-0.17	X	0.19	-0.17
Log total protein		-0.16				-0.17	X		-0.19
Log albumin		-0.27			-0.16		X		-0.17
Log BUN	0.16		0.34	0.19			X		
Creatinine	0.19	-0.40	0.23				X		-0.17
Log B/C ratio			0.17				X		
Iron			0.20	-0.15			X		
RBC		-0.59					X		0.18
WBC						0.29	X		0.21
Lymphocytes							X		0.16
% Monocytes							X	-0.27	-0.27
1979									
Log triglycerides	0.21			0.40				X	
Cholesterol	0.35			0.19				X	
Log GGTP	0.18	-0.28	0.19	0.23				X	
Log alk. phos.				0.14				X	
Direct bilirubin		-0.16				-0.15		X	-0.14
Log blood glucose	0.29		0.16		0.38			X	
Globulin				0.27			0.15	X	
Log A/G ratio	-0.21			-0.24			-0.16	X	
Log BUN	0.20		0.34	0.23				X	
Log B/C ratio	0.26		0.30					X	
Monocytes						0.19	-0.21	X	0.21
% Monocytes							-0.24	X	0.23

ranges. For these criteria, the only variables having statistical significance outside the normal ranges were the 1976 percent lymphocytes and the 1979 percent monocytes. For all other parameters the observed associations with log PCB levels reflected variations within the normal laboratory ranges.

Figures 3 and 4 show partial residual plots for two laboratory variables, log total bilirubin in 1976 and the percent monocytes in 1979, as calculated at the end of the stepwise regression, plotted against log serum lipid LPCB. They represent plots of a predictor variable against the dependent variable with the "effects" of all other predictor variables statistically removed (33). For the log total bilirubin data of Figure 3, the partial r was -0.22 ($p = 0.01$) and β_1 about -0.09 log units/decade of LPCB (Table 6). For 2.2 decades of LPCB, the range of the β_1 product was -0.07 to -0.33 (mean = -0.2). When controlled for confounders, all study data (Fig. 3) fell between 0.1 and 1.0 mg/dL (mean = 0.3 mg/dL), which is within the normal range (Table 1).

As shown in Figure 4 the 1979 percent monocyte data were more tightly grouped (partial $r = 0.28$), and the β_1 estimate was 1.38%/LPCB decade. For the 2.5 decade range of LPCB, the range of β_1 products corresponded to an increment in percent monocytes of 1.8 to

6.2% (mean = 3.5%). Inspection of the histogram along the monocyte axis indicates a range of percent monocytes from 5.5 to 15.5% (mean = 10.5%) rather than the normal range of 0 to 8% (Table 1).

Discussion

PCB Levels in the Study Population

This investigation has shown that certain former operations in capacitor manufacturing presented high exposures to PCBs, particularly during the 1954-1977 period when the more volatile lower PCBs (Aroclor 1242 and 1016) were in extensive use. During this period PCB air levels in the affected working areas were probably at least the 690 $\mu\text{g}/\text{m}$ observed in 1975, accompanied by extensive dermal contact as well.

In our study population, selected so as to include those working in or near the plant PCB exposure zone, the mean serum lipid LPCB level in 1976 (Table 3) was estimated to be 93 ppm (5-95% range, 15-560 ppm), adjusted for a factor of 10 analytical error. This serum lipid value corresponded to a mean body burden of 2.0 g (0.3-12.3 g) for the population mean body weight of 77 kg (22 kg of fat). These retained LPCBs were com-

Table 8A. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum *p*, *p'*-DDE, as determined by three regression procedures: log gross serum DDE.*

Log gross serum DDE										
Dependent variable*	r	Simple regression			Multiple regression			Step regression		
		$\hat{\beta}_1$	Confid. limits		$\hat{\beta}_1$	Confid. limits		$\hat{\beta}_1$	Confid. limits	
			5	95		5	95		5	95
1976										
Log triglycerides	2.13	0.08*	0.05	0.11	0.07*	0.03	0.10	0.08*	0.05	0.11
Cholesterol	251.3	12.7*	5.05	20.4	8.37	-0.13	16.9	10.1*	2.00	18.2
Log GGTP	1.09	0.04*	0.002	0.08	0.02	-0.02	0.06	0.03	-0.01	0.07
Log alk. phos.	1.42	0.04*	0.02	0.06	0.04*	0.02	0.07	0.04*	0.02	0.07
Log total protein	0.86	0.002	-0.002	0.006	0.009	-0.001	0.009	0.005*	0.001	0.009
WBC	7.02	0.33*	0.08	0.57	0.41*	0.12	0.70	0.35*	0.08	0.62
Lymphocytes	2.33	0.23*	0.11	0.34	0.30*	0.16	0.44	0.26*	0.13	0.40
% Lymphocytes	33.8	1.42	-0.11	2.95	2.04*	0.17	3.91	1.37	-0.38	3.11
% Monocytes	4.38	-0.36*	-0.70	-0.02	-0.40	-0.80	0.004	-0.46*	-0.83	-0.08
1979										
Log triglycerides	2.16	0.31*	0.21	0.41	0.28*	0.18	0.38	0.30*	0.21	0.39
Cholesterol	238.2	48.6*	25.8	71.5	32.6*	7.56	57.6	30.4*	6.07	54.7
Log alk. phos.	1.47	0.09*	0.04	0.15	0.09*	0.03	0.15	0.10*	0.04	0.16
Log total protein	0.86	0.01	-0.004	0.02	0.01*	0.001	0.03	0.01	-0.001	0.03
Log albumin	0.64	-0.02*	-0.03	-0.01	-0.006	-0.02	0.01	-0.006	-0.02	0.01
Globulin	2.92	0.30*	0.10	0.50	0.23*	0.02	0.44	0.24*	0.04	0.43
Log A/G ratio	0.18	-0.06*	-0.09	-0.02	-0.03	-0.07	0.01	-0.03	-0.07	0.01
Serum Ca	9.67	-0.02	-0.22	0.18	-0.10	-0.33	0.13	-0.08	-0.29	0.13
Serum Iron	108.6	-10.3	-24.3	3.68	-10.0	-25.5	5.50	-8.81	-22.9	5.30

*See Table 6 footnotes.

Table 8B. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum *p*, *p'*-DDE, as determined by three regression procedures: log serum lipid DDE.*

Dependent variable*	Simple regression			Multiple regression			Step regression		
	$\hat{\beta}_1$	Confid. limits		$\hat{\beta}_1$	Confid. limits		$\hat{\beta}_1$	Confid. limits	
		5	95		5	95		5	95
1976									
Log triglycerides									
Cholesterol									
Log GGTP									
Log alk. phos.									
Log total protein									
WBC									
Lymphocytes									
% Lymphocytes									
% Monocytes									
1979									
Log triglycerides	0.08	-0.04	0.20	0.06	-0.06	0.18	0.07	-0.04	0.19
Cholesterol	-3.10	-29.7	23.5	-20.8	-47.9	6.34	-21.6	-47.9	4.76
Log alk. phos.	0.07*	0.002	0.13	0.07	-0.002	0.13	0.08*	0.01	0.14
Log total protein	-0.003	-0.02	0.01	0.001	-0.01	0.02	0.001	-0.01	0.02
Log albumin	-0.02*	-0.04	-0.004	-0.01	-0.03	0.008	-0.01	-0.03	0.007
Globulin	0.15	-0.08	0.38	0.07	-0.16	0.30	0.08	-0.15	0.30
Log A/G ratio	-0.04	-0.08	0.002	-0.01	-0.06	0.03	-0.02	-0.06	0.03
Serum Ca	-0.17	-0.39	0.06	-0.24*	-0.48	-0.001	-0.22	-0.45	0.008
Serum Iron	-19.7*	-35.0	-4.43	-19.6*	-36.0	-3.20	-17.5*	-33.1	-2.00

*See Table 6 footnotes.

posed almost entirely of PCB isomers with gas chromatographic peaks having retention times (relative to DDE = 100) of 37, 71 and 84 (27,34), the other LPCB components of Aroclors 1016 and 1242 being much more readily metabolized in the human. Regression studies

of serum lipid LPCB values with length of service indicated no significant statistical association, so that steady state levels appeared to have been reached within the first few years of employment. Thus, the levels of retained LPCBs observed in 1976 could have been rep-

Table 8C. Regression and correlation coefficients for 1976 and 1979 clinical variables showing at least one significant association with a measure of serum *p, p'*-DDE, as determined by three regression procedures: independent variables.

Dependent variable	Independent variables								
	Partial <i>r</i>								
	Age	Sex	SPG	BMI	DS	SC	JS	FNF	Log (DDE)
1976									
Log triglycerides				0.29	0.27				0.38
Cholesterol	0.31			0.20					0.19
Log GGTP		-0.19		0.17				0.25	
Log alk. phos.									0.31
Log total protein	-0.23					-0.17			0.16
WBC						0.25			0.20
Lymphocytes					-0.16				0.33
% Lymphocytes									
% Monocytes						0.16		-0.25	-0.21
1979									
Log triglycerides	0.21			0.40					
Cholesterol	0.35			0.19					
Log alk. phos.				0.14					0.18
Log total protein	-0.14			0.23		-0.19			
Log albumin	-0.21						-0.15		
Globulin				0.27			0.15		
Log A/G ratio	-0.21			-0.24			-0.16		
Serum Ca					0.15				
Serum Iron		-0.20							-0.17

*See Table 6 footnotes.

Table 9. Regression coefficients for 1976 and 1979 clinical variables showing at least one significant association with a estimate of relative exposure to PCB in 1976 (EXE), as determined by three regression procedures.*

Dependent variable*	N	$\bar{x}$	Simple regression			Multiple regression			Step regression			Partial (EXE)
			β_1	Confid. limits		β_1	Confid. limits		β_1	Confid. limits		
				5	95		5	95		5	95	
1976												
Cholesterol	193	251.3	7.86	-1.33	17.0	9.62	-0.16	19.4	10.5*	1.26	19.7	0.18
Log GGTP	192	1.09	0.03	-0.01	0.10	0.06*	0.01	0.10	0.06*	0.01	0.10	0.20
Log total bilirubin	194	-0.34	-0.04*	-0.08	-0.01	-0.05*	-0.09	-0.02	-0.05*	-0.08	-0.01	-0.20
Direct bilirubin	193	0.15	-0.01	-0.02	0.002	-0.02*	-0.03	-0.001	-0.02*	-0.03	-0.001	-0.17
Log blood glucose	193	2.01	-0.01*	-0.02	-0.004	-0.01	-0.02	0.003	-0.01	-0.02	0.001	
Log A/G ratio	191	0.21	0.02*	0.001	0.03	0.01	-0.005	0.03	0.01	-0.004	0.03	
Serum Na	192	139.5	-0.10	-0.55	0.34	-0.54*	-1.02	-0.06	-0.53*	-0.98	-0.08	-0.18
Serum iron	192	112.1	-6.35*	-12.3	-0.36	-3.89	-10.8	3.00	-4.23	-10.8	2.30	
Lymphocytes	153	2.33	0.14	-0.01	0.23	0.19*	0.02	0.36	0.15	-0.01	0.31	
Monocytes	153	0.31	-0.01	-0.05	0.02	-0.01	-0.04	0.03	-0.01	-0.04	0.03	
% Monocytes	153	4.38	-0.34	-0.74	0.06	-0.35	-0.82	0.11	-0.46*	-0.90	-0.02	
1979												
Cholesterol	174	238.5	4.72	-1.09	13.5	4.83	-3.91	13.6	4.94	-3.43	13.3	
Log GGTP	174	1.20	0.01	-0.03	0.06	0.02	-0.02	0.07	0.02	-0.02	0.07	
Log total bilirubin	174	-0.22	-0.02	-0.05	0.01	-0.03*	-0.06	-0.001	-0.03*	-0.06	-0.004	-0.18
Direct bilirubin	174	0.14	-0.01	-0.02	0.01	-0.01	-0.03	0.003	-0.01	-0.03	0.001	
Log blood glucose	174	2.00	-0.004	-0.01	0.01	-0.001	-0.01	0.01	-0.002	-0.01	0.01	
Log A/G ratio	174	0.18	-0.003	-0.02	0.01	-0.006	-0.02	0.07	-0.005	-0.02	0.01	
Na	174	139.4	-0.05	-0.46	0.37	-0.02	-0.43	0.40	-0.02	-0.43	0.39	
Iron	172	108.5	-0.96	-6.17	4.25	-0.78	-6.17	4.62	-0.78	-6.17	4.62	
Lymphocytes	175	2.09	-0.03	-0.14	0.68	-0.03	-0.16	0.09	-0.03	-0.14	0.09	
Monocytes	175	0.48	0.04*	0.001	0.08	0.04*	0.004	0.08	0.05*	0.01	0.08	0.18
% Monocytes	175	6.9	0.58	0.14	1.03	0.61*	0.17	1.05	0.64*	0.20	1.07	0.22

*See footnotes to Table 6.

representative of those present throughout the Aroclor 1242 and 1016 periods of use.

The mean serum HPCB level in 1976 was estimated to be 8 ppm (2-34 ppm), corresponding to a mean body

burden of 0.2 g (0.04-0.7 g). These HPCBs were composed primarily of penta- and hexachlorobiphenyl isomers (27,34,35) resulting either from exposures to Aroclor 1242 (which contained a few percent of the lower

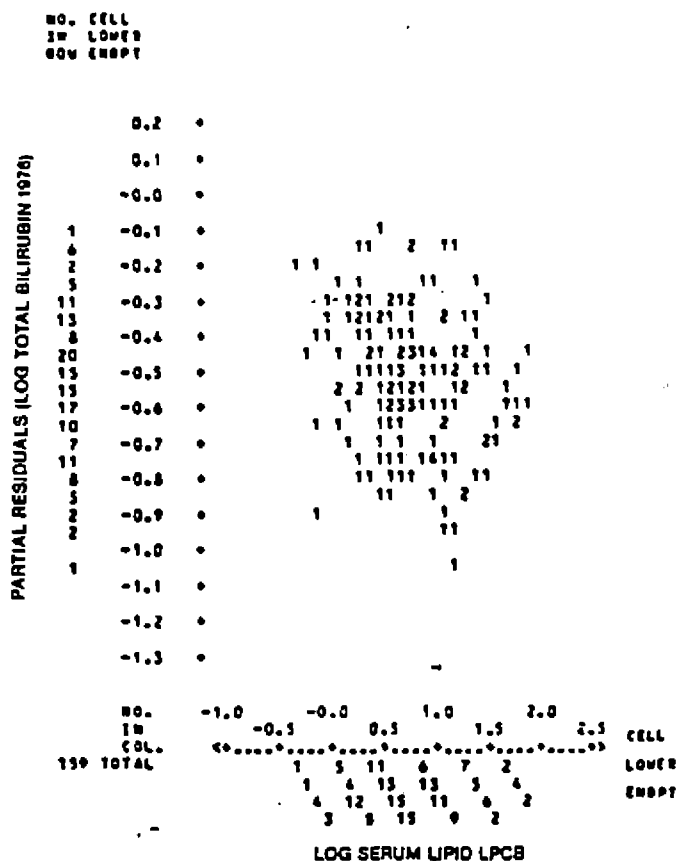


FIGURE 3. Partial residuals for log total bilirubin in 1976 following final step regression (Table 6) vs. log serum lipid LPCBs. Histograms are shown along each axis. The number of values in the cells are given by the numerals.

HPCBs), or from earlier exposures to Aroclor 1254. Their levels were significantly associated with length of service, so that the upper 5% of HPCB levels observed in 1976 (long service, directly exposed workers) may be representative of the exposed population in 1954, at the end of the period when Aroclor 1254 was the major dielectric fluid used.

The Aroclor 1242 values reported to us by the analyst were approximately 4 times the calculated LPCB values (Table 3). We have shown elsewhere that the minimum initial concentrations of Aroclors 1016 plus 1242 required to account for the most persistent LPCB peaks were about 7.5 times the residual LPCB levels (27). Thus, the minimal LPCB uptake by the study population may be estimated as 15 g (2.5–92 g). This estimated uptake is a minimum since even the most persistent LPCB peaks have a finite clearance rate (unpublished observations). The longer service employees could have absorbed several times this minimal PCB uptake, but until better data on PCB clearance becomes available, actual cumulative LPCB uptakes cannot be estimated more precisely.

The mean LPCB body burden in 1979 (29 months after discontinuance of major exposure) was estimated as 0.4 g (0.7–2.0 g), indicating a clearance of 80%. The serum lipid HPCB means in 1976 and 1979 were within the

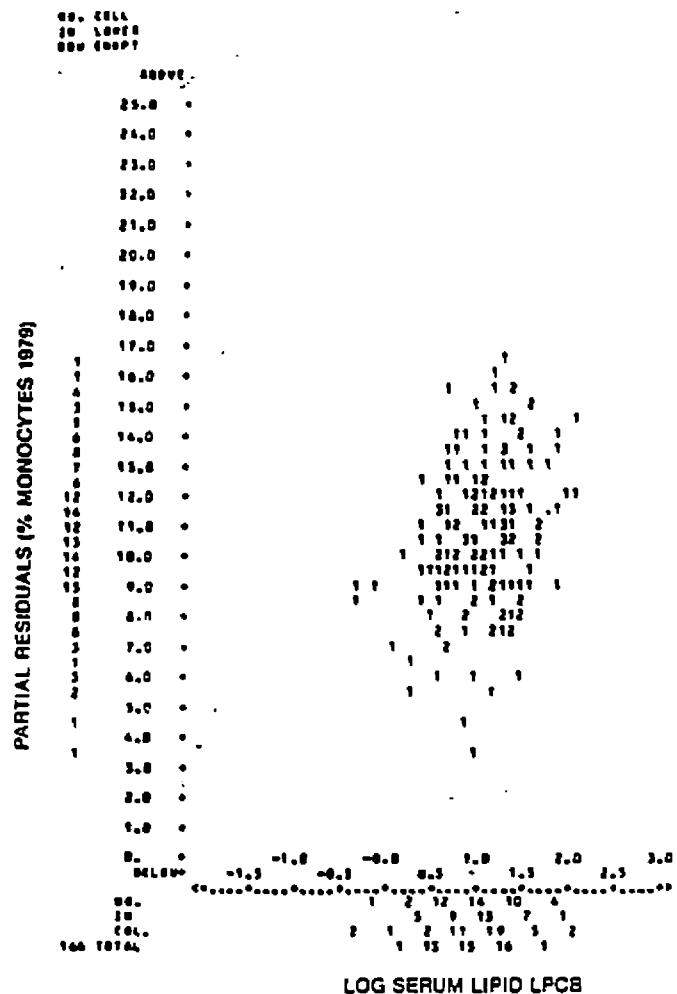


FIGURE 4. Partial residuals for % monocytes in 1979 following final step regression (Table 6) vs. log serum lipid LPCBs. Histograms are shown along each axis. The number of values in the cells are given by the numerals.

error band of the analytical technique (27) and a conclusion of significant clearance is probably unwarranted. Chen (35) has reported clearance rates for various pentachlorobiphenyl isomers in Taiwanese Yusho patients that appear to be at least 10-fold greater than we observed in capacitor workers (27); however, such clearance might be related to P-448 oxidase induction by PCDFs in the Yusho patients. Although these estimates of PCB fat levels and uptakes are only approximate, they serve to define the dose ranges within which the observed responses can be ascribed.

PCB Effects on Serum Lipids and Serum Enzymes

Previous investigators have reported statistical associations between log gross serum levels of PCBs and the serum levels of triglycerides, total cholesterol and certain serum enzymes. Our findings were in general agreement with such reports. We found significant associations of log serum triglycerides and total cholest-

terol with every measure of log gross serum PCBs and DDE in the final step regressions. Similar associations were found for log GGTP, and in some cases for log SGPT, with log gross serum PCBs, and for log alkaline phosphatase with log gross serum DDE.

It is now evident, however, that such associations arise because the level of PCBs in the serum is itself determined by that of the serum lipids (23,24). When the PCB concentrations were expressed as levels in serum lipids, which would be expected to correlate with the pharmacological activities (24,25), all the associations between serum lipids or enzymes and log gross serum LPCB, HPCB or DDE disappeared except for those between log GGTP and log PCBs, and between log alkaline phosphatase and log DDE. Similarly, Chase et al. (13), who reported associations with gross serum PCBs, found no significant correlation between either serum triglycerides or SGOT and the adipose tissue fat biopsy PCB levels. Although elevated levels of serum triglycerides, total cholesterol and SGPT were found in our study population (Table 3), serum GGTP levels were generally in the normal range, and the regression studies indicated stronger associations with obesity (body mass index).

PCB Effects on Microsomal Enzymes

Elevated serum GGTP levels have been prominently mentioned in the literature as an index of microsomal enzyme induction in the human (36-40). Recent studies (41), however, have in part disputed this conclusion. In their review of environmental hepatic injury, Popper et al. (42) found only meager evidence of substantiated chronic hepatic effects. They concluded that conventional liver function tests were of limited value in detecting hepatic abnormalities and that the evidence so far indicates that too many other processes influence GGTP activity in man to make it a useful index of induction. The clinical implications of elevated GGTP levels in man are reviewed by Guzelian elsewhere in this symposium.

However, the interpretation of the relationship between serum GGTP and serum lipid PCBs as evidence of microsomal enzyme induction is strengthened by the finding of strong inverse statistical associations between both direct and total bilirubin levels and serum lipid PCBs in 1976 during the period of active PCB exposure. A weak residual association between serum lipid HPCB and direct bilirubin (partial $r = 0.14$) was found in 1979 when the mean total bilirubin (mostly unconjugated) had risen from 0.46 to 0.61 mg/dL without change in the mean direct bilirubin (conjugated form) (Table 1).

Since the original observations of Yaffe et al. (43) on the therapeutic use of phenobarbital to enhance glucuronide-conjugating capacity in infant hyperbilirubinemia, a substantial literature has developed linking drugs (36,44) and other xenobiotics (45,46) to induction of microsomal enzymes, including enhanced glucuronyl transferase, resulting in increased conjugation and ac-

celerated hepatic elimination of bilirubin. D-Glucuronic acid is the main excretory product of the glucuronic acid conjugation pathway and its urinary level also has been advocated as a measure of enzyme induction (47-50). Drugs and chemicals inducing microsomal enzymes are often metabolized by the induced oxidases (32), and it appears likely that such induction would accelerate clearance of PCBs as well as bilirubin (49,51).

Hirayama et al. (52) reported serum total bilirubin levels of 0.87 ± 0.33 mg/dL in 257 normal controls and 0.48 ± 0.26 mg/dL in 121 Yusho patients, indicating a 46% decrease in the latter. However, the observations were made at a time when the PCB levels had declined to background values, so that the pharmacologically active agents present were probably the PCDFs. Induction of glucuronyl transferase by Aroclor 1242 and 1016 has been reported in rats (16,53), as has also that of demethylases (16,53), aniline hydroxylase, (53) and cytochrome P-450 (16,53), but not that of the P-448 cytochrome (16).

Burse et al. (54) have shown that rats fed 100 ppm of Aroclor 1242 or 1016 (3.9-6.6 and 3.5-6.9 mg/kg/day) reach equilibrium adipose tissue fat concentrations of 35 to 143 or 69 to 236 ppm, respectively, at 6 months, levels in the range of those observed in this study (Table 3). Similar levels in rats were also reported by Goldstein et al. (53), who found a 3- and 12-fold increase in liver glucuronyl transferase activity with Aroclors 1016 and 1242, respectively.

The most compelling evidence for microsomal enzyme induction in man is a response to drug administration (42). In 1977, Alvares et al. (16) reported antipyrine half-times reduced 31% over matched controls in five capacitor workers with PCB exposures of 4 to 16 years drawn from the same plant population as the present study. The effect was statistically significant ($p < 0.005$) and the half-times were significantly less than the average values of much larger groups of normal healthy subjects. The statistical associations of the present study, taken together with the findings of Alvares et al., appear to indicate induction of the microsomal enzymes GGTP, glucuronyl transferase, and P-450 oxidase in the study population during active exposure in 1976. The enzyme inductions appeared to be smaller than those in rats carrying similar levels of lipid LPCBs and to have become virtually undetectable by 1979.

PCB Effects on Hematological Parameters

The findings of significant associations between log serum lipid PCBs and some hematological variables was unexpected because Maroni et al. (14) reported normal hematology including WBCs and differentials and no abnormal reports in occupationally exposed PCB workers have been mentioned by others (11-13,15,17). In 1976 the clinical reports (Table 2) suggested a slight decline in PMNs with some increases in lymphocytes, monocytes and eosinophils, and normal values for RBCs, hemoglobins and hematocrits.

Interpretations of these data are difficult because of the shared associations with DDE and the colinearities with either total or direct bilirubin or both. For the associations with log total bilirubin, the partial r values were: RBC, +0.19; lymphocytes -0.22; and creatinine, 0.24; for direct bilirubin, they were: phosphate, -0.18; and creatinine, 0.23. We tend to the interpretation that these variables are correlated with the enzyme induction process.

In 1979, although both the monocytes and eosinophils were only marginally elevated in the study population based on clinical reports (Tables 1 and 2), the statistical association of serum PCB levels and the monocyte counts was strong.

Because of the absence of a monocytosis in 1976, its lack of association with either DDE or total or direct bilirubin in 1979, and its absence among retirees in 1979, we hypothesized that the effect might be related to a new exposure in the workplace, perhaps to the PCB-substitute dielectric. However, we recently studied 54 workers with no prior PCB exposure who were currently exposed to the substitute and found no monocyte elevations. Although a number of solvents were in use in the environment in 1979, the monocytosis was mild compared to that observed by Minot and Smith (55) in the case of tetrachlorethane exposure, where the monocyte levels were elevated 20 to 40%. The effect of the change from the manual (1976) to automated differential analysis (1979) is unknown. We have also hypothesized that the monocytosis observed in 1979 might be related to the increased incidence of chronic obstructive lung disease, heavy smoking or concurrent respiratory infections. We are currently studying the associations between the spirometric variables (FVC, FEV, FEV/FVC) and the hematological parameters in the study population and are restudying the entire population, which should cast further light on any such relationships.

Clinical Consequences of PCB Exposure

These findings differ from those of most other recent studies of environmentally or occupationally exposed populations in offering evidence of microsomal enzyme induction, which is consistent with the extensive LPCB clearance also observed in these highly exposed workers. The evidence is statistical in nature and the associated parameters remained within their normal clinical ranges, except possibly for the lymphocytes in 1976 and the monocytes in 1979. The effects were therefore physiological rather than pathological and appeared to subside following the cessation of PCB use. The long-term consequences of such enzyme induction are obscure (42).

The present clinical health of the study population appears to meet community medical standards. Despite the prevalence of cardiovascular risk factors (obesity, elevated cholesterol levels, smoking, etc.) the mortality experience has been normal. The paucity of clinical abnormalities is consistent with laboratory studies in rats involving chronic administration of Aroclor 1242 and

1016, producing tissue fat levels comparable to the serum lipid PCB levels observed here. Such studies (54) have shown no overt symptoms of clinical poisoning and no pathological evidence of liver damage. The production of serious liver damage in rats (56) requires the use of a largely nonmetabolizable PCB, such as Aroclor 1260, at a cumulative dose of 2.5 g/kg, which would result in tissue lipid HPCB levels above 10,000 ppm, as compared to those in our study population of 8 ppm in 1976 and 5 to 6 ppm in 1979. It is evident, therefore, why the serious hepatic effects in the test rat could not be observed in man.

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Spirometric Findings in Capacitor Workers Occupationally Exposed to Polychlorinated Biphenyls (PCBs)

Richard W. Lawton, MD; Marie R. Ross, RN; and Joseph Feingold, MD

Spirometric findings (forced vital capacity [FVC], forced expiratory volume at one second [FEV₁], FEV₁/FVC) in a population of capacitor workers with occupational exposure to polychlorinated biphenyls (PCBs) are described during active PCB use (1976) and following the PCB ban (1979 and 1983). The initial finding of restrictive impairment (16%) in 1976 was not supported by chest roentgenogram findings, nor confirmed in 1979 and 1983, and was interpreted as artifactual due to test operator inexperience and inadequate expiratory efforts. Obstructive impairment was consistently found in 15% of the total population in 1976 and 1979. A history of respiratory illness and/or symptomatology and reduced FEV₁/FVC was correlated with PCB exposure and serum PCB levels (lower homologs) in females in 1976, but not in males. Smoking was correlated with reduced FEV₁ values. No correlation of spirometric variables with past exposure or serum PCB levels was found for either sex in 1979.

In spirometric studies of a group of capacitor workers (N = 243), some of whom had high direct occupational exposure to PCBs, Warshaw et al¹ found a substantial prevalence of reduced vital capacity (FVC < 79.5% of predicted value). The prevalence (14%) was

reported by them as equivalent to that of asbestos workers (12.1%). Of those showing FVC reductions, 80% showed a restrictive pattern (FEV₁/FVC > 0.70) without radiologic changes. PCBs were not reported as acute direct pulmonary irritants, although eight-hour time-weighted average air levels in the workplace areas of PCB use varied from 0.6 to 11.0 mg/m³.²

The present paper reports a spirometry study of capacitor workers, drawn from the same plant population as that of Warshaw et al, but involving only workers with current occupational PCB exposure in 1976. Spirometry was repeated in 1979, 1981, and 1983 and provided longitudinal data on a selected population.

Methods and Materials

The study population consisted of all capacitor workers with direct work-related PCB exposure in two plants in upper New York state. This population, when selected in 1976, consisted of 194 workers (152 males, 42 females) representing approximately 10% of the work force. Ages extended from 22 to 66 years and service times from 1 to 35 years. The cohort was examined in 1976, 1979, 1981, and 1983. Exposure was defined in three categories: (1) high exposure: jobs requiring dermal contact in high air level zones (handling and sealing wet capacitors, capacitor salvage and repair); (2) medium exposure: jobs requiring brief high exposure and contact such as maintenance men; and (3) low exposure: jobs not involving dermal contact but in or at the periphery of the high-exposure zone.

The initial examination consisted of a medical history, physical examination, chest roentgenograms, ECG, sequential multichannel autoanalyzer (SMA-26) blood analysis, hematology, urinalysis, and spirometry. Body weight was obtained in light indoor clothing and height

From the Biological Sciences Branch, Corporate Research and Development, General Electric Company, Schenectady, NY (Dr Lawton, R&D staff); Capacitor Products Department, General Electric Company, Hudson Falls, NY (Ms Ross, Occupational Health Nurse; Dr Feingold, Plant Physician. Dr Feingold is retired and currently in the practice of internal medicine at 31 East St, Fort Edward, NY 12928).

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Address correspondence to: General Electric Company, Corporate Research and Development Center, PO Box 8, Bldg K-1, Room 3B12, Schenectady NY 12301 (Dr Lawton).

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was determined without shoes. Subsequent examinations consisted of blood workup, changes in body weight and blood pressure, and spirometry. Chest roentgenograms, ECG, and physical examination were repeated in 1983. Smoking classification (smokers, ex-smokers and nonsmokers) was obtained in 1976. Detailed smoking histories (cigarettes per day, years smoked, etc) were not obtained until 1979 ($N = 165$). These were generally confirmed in 1983 and the 1979 data were used throughout the analysis with no account taken of the few reports of change in habit over the period. Chest roentgenograms were classified according to the International Labor Organization classification of radiographs (form OMB No. 68-5 1322). With two exceptions all roentgenograms with positive findings were classified in section 4.

Serum PCB levels were obtained in 1976 and 1979 (analysed by Hazleton Laboratories America, Inc, Madison, WI) using methods previously described.³ Pulmonary function was evaluated in 1976 using a Vanguard spirometer with a disposable filter paper flow sensor (Life Support Engineering Corp, Woburn, MA). In 1979 an updated version (Vanguard DS502) with a preprogrammed computer printout was used. Measurements were made in the standing position and the nose closed with the fingers. The calibrating source was a VS300 3-l syringe and calibration conducted at various volumes and rates as recommended.⁴ For each worker the maximum expiratory volume-time curve was recorded and examined for freedom from test artifacts.⁵ At least three trials were performed by each worker and reproducibility of the expiratory effort was accepted at the 10% level.

Measurements were made of forced vital capacity (FVC), the forced expiratory volume at one second (FEV_1) and the ratio (FEV_1/FVC) using the highest test of the three trials. The data were evaluated as the percent of predicted values using the tabulated predictions of Knudson et al.^{6,7} The spirometric patterns were classified as restrictive ($FVC < 80\%$ of predicted, $FEV_1/FVC > 70\%$); obstructive ($FVC \geq 80\%$ of predicted, $FEV_1/FVC \leq 70\%$); or mixed ($FVC < 80\%$ of predicted, $FEV_1/FVC \leq 70\%$).

Initially (1976) the nurse conducting the test had had little spirometric training and only subsequently was certified (1978) for pulmonary screening. Retrospective review of the 1976 expiratory spiograms indicated 15 tests (7.7%) to be unacceptable due to technical error. Subsequently, only two workers' test results were unacceptable: one due to thoracic arthritis and another due to poorly fitting dentures. Nine workers' test results were unacceptable in 1976 but were acceptable in 1979.

Statistical analysis was performed on a Honeywell Series 600/6000 computer using available time-sharing applications programs.⁸ Regression analyses were conducted using STATPAC, a versatile statistical package⁹ for distribution plotting and the derivation of coefficients and correlations by multiple stepwise regression. An incremental F-ratio of 3.9 was used for entering and removing variables so that variables significant at the 5% level were included. Only one marginal association

was found and this was treated as significant. PCB exposure was described in terms of the exposure category, treated as a dummy variable, or the serum PCB level, either as reported, or as the concentration in total serum lipids.³

As a consequence of dropouts due to retirement or employee separation, rejected tests, refusal of the procedure, or death, the number and composition of the participating population changed during the three examination periods. For these reasons, and because of incompleteness of detailed smoking data, the analysis focused on 136 workers for whom complete data were available for the 1976, 1979, and 1983 time periods. In addition, 93 workers were examined at some point in 1981 so that a total of 80 workers had four sets of measurements. These subgroups provided a longitudinal assessment of the spirometry changes with time and of the reliability of the procedure. The entire available population was used to assess abnormal spirometric findings and for the relations with serum PCB levels.

Results

Workers in the study population were overweight (50% of the workers had body weights above the normal "desirable" range for large-framed individuals¹⁰) and heavy smokers. Those who smoked or had smoked (71.4% of males, 54.2% of females) averaged a pack a day for 18 to 20 years.

In 1976 there were seven cases of clinically recognized emphysema and 12 workers were told by their physicians they had chronic bronchitis, although only two complained of current shortness of breath, cough, or sputum production. Past histories of significant pulmonary infections were reported in 16 cases. Chronic upper respiratory tract infections and allergies were prevalent. Four workers (heavy smokers) reported leukoplakia and/or laryngeal polyps. On chest roentgenogram examination emphysema was suspected in six cases. The predominant finding was evidence for past pulmonary infection (granulomata, calcifications, scarring). A coin lesion (malignant) was discovered in one worker. Evidence for fibrosis was found in only two workers. One worker (with carcinoma of the lung) showed bilateral circumscribed pleural thickening; another worker showed old healed pleural thickening at the left base. Mean 1979 serum PCB levels were elevated 35 to 40 times the normal background community levels in humans. The levels for PCBs were higher in the female subgroup.

The Figure shows spirometry data converted to percent of predicted value for 80 workers who had measurements made at four periods during this study. The plotted points are means $\pm$ the 95% confidence limits for the population average. For the males, ($N = 75$) the mean FVC value rose between 1976 and 1979 (4.53 L to 4.90 L) and then declined (4.70 L in 1983). With the smaller accompanying change in FEV_1 , the FEV_1/FVC ratio fell in 1979 and then returned to its 1976 value. However, as indicated in the Figure, only the FEV_1 population average appeared to be significantly less

than 100% of the predicted value in 1976. These data indicated a continuing improvement in the reliability of the measurements with experience of both the operator and the workers.

Using the predictions of Knudson et al.,⁶ workers were classified in restrictive ($FVC \leq 80\%$; $FEV_1/FVC \geq 70\%$) and obstructive ($FEV_1 \leq 80\%$; $FEV_1/FVC \leq 70\%$) cat-

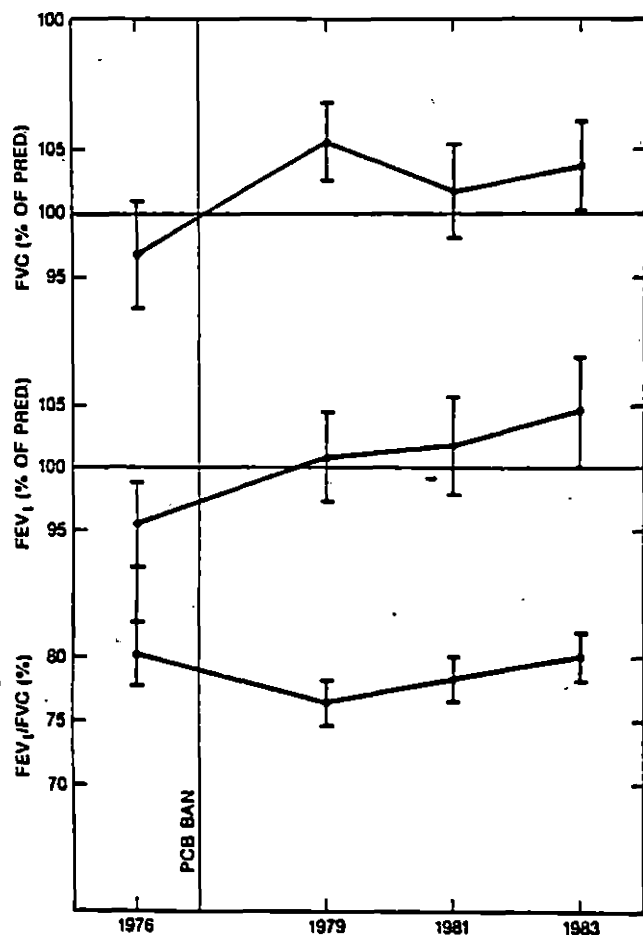


Figure. FVC, FEV₁, and FEV₁/FVC as percent of predicted value⁶ for portion of study population with four spirometry tests (N = 80). Means and 95% confidence limits.

egories (Table). In 1976 for the total population (N = 179) we found that 16.2% of the population showed restrictive impairment. In 1979 the percent of the population showing this finding declined to 2.9%. In contrast, the obstructive category was relatively constant (15.6% and 15.3%) with 2.2% to 3.4% of the population showing a mixed result (FVC and FEV₁ both $\leq 80\%$ and $FEV_1/FVC \leq 70\%$). Obstructive defects were more prevalent in smokers and ex-smokers. Of those with $FEV_1/FVC \leq 70\%$ about 70% had values between 65% and 70% and the ventilatory impairment was considered mild. Four of the 25 workers not returning for the test in 1979 were known to have clinical chronic obstructive lung disease. Because the study dropouts in 1983 made up such a large percentage of the population (21%), scoring for these data provided a lower estimate of the obstructive category.

Using multiple stepwise regression we examined the significant partial correlations of the measured spirometric parameters with the conventionally used variables (sex, age, body height), as well as those of interest in this study (smoking, respiratory history, and PCB exposure). Although the number of workers with satisfactory spirometry and complete data varied for the three examinations, we found strong and complete regressions for FVC and FEV₁, but incomplete and weaker equations for FEV₁/FVC. Spirometric variables were inversely associated with smoking in all cases except FEV₁/FVC in 1976. Body weight was inversely associated with FVC in 1979 and 1983. This latter relation was characteristic of the male subpopulation. The presence of a history of respiratory infection and/or symptomatology was significantly associated with a decreased FEV₁ and FEV₁/FVC in 1979 and 1983. High exposure to PCBs in the workplace, as measured either by the exposure category or the serum PCB level, was significantly associated with a decreased FEV₁/FVC in 1976, a period of active PCB use. However, this association of exposure and FEV₁/FVC was found only for the female subpopulation. There were no significant associations for the serum PCB level and the spirometric parameters in 1979 for either sex.

The Pearson product-movement correlation coefficient

TABLE
Restrictive, obstructive and mixed spirometric findings in total population in 1976 and 1979 using predictions of Knudson et al.⁶

	1976						1979					
	Male		Female		Total		Male		Female		Total	
	Smokers and Ex-smokers	Non-smokers	Smokers and Ex-smokers	Non-smokers	No.	%	Smokers and Ex-smokers	Non-smokers	Smokers and Ex-smokers	Non-smokers	No.	%
N	103	39	22	15	179	100.0	94	38	22	16	170	100.0
Restrictive ($FVC \leq 80\%$; $FEV_1/FVC \geq 70\%$)	19	6	2	2	29	16.2	2	0	1	2	5	2.9
Obstructive ($FVC \geq 80\%$; $FEV_1/FVC \leq 70\%$)	14	3	9	2	28	15.6	14	2	9	1	26	15.3
Mixed ($FVC \leq 80\%$; $FEV_1/FVC \leq 70\%$)	4	0	1	1	6	3.4	2	0	2	0	4	2.4

cients for the constant population ($N = 136$) in 1978 and 1979 indicated an association of exposure with respiratory history and symptomatology in females, although the relation was marginally significant ($P = 5.12\%$). In males we found the respiratory history to be significantly associated with smoking. Smoking was also associated with a reduced FEV_1 in males in 1976 and 1979 but only for females in 1979.

Discussion

Medical surveillance of a group of capacitor workers directly exposed to PCBs was undertaken in 1976 to assess the workers' general health. The medical examination included spirometry, which was repeated in 1979 and 1983, and on a part of the group in 1981. We found pulmonary-function testing to be one of the most difficult procedures to perform well in the industrial medical setting. The procedure requires a trained and certified nurse or technician, functional and properly calibrated equipment, and motivated and cooperative workers if adequate data are to be obtained. These conditions were not fulfilled at the inception of this study: the nurse had little spirometric training and testing experience and worked in cramped quarters with new equipment. The test was new for the workers whose motivation was uncertain, given the intense media coverage of PCBs at the time. As a consequence only 179 out of 194 workers tested (92%) had apparently satisfactory forced expiratory volume-time curves on retrospective review. Following nurse certification and repeated worker experience with the procedure, unsatisfactory data were obtained in 1% or less of tested cases in 1979, 1981, and 1983.

Because of the technical deficiencies in the spirometry procedures and the uncertainties associated with the serum PCB measurements in 1976,³ we were inclined to reject the data. However, these observations were obtained during the period of active PCB use and were characterized by high serum PCB levels in the workers. In addition, the observations coincided in time with those of Warshaw et al.¹ In their studies (1976), as well as in ours, reduced FVCs were observed. FVCs $< 80\%$ of predicted with normal FEV_1/FVC ($> 70\%$) were found in 14% of the population studied by Warshaw et al and in 16.2% of our study population. In both studies there were no radiologic evidences of pulmonary fibrosis to account for the restrictive impairment observed.

In our study, based on longitudinal observations, we believe the finding to be artifactual. FVC values as percent of predicted for the population in 1976 were normally distributed over the range, indicating a systematic decrease, which could have resulted from generally poor coaching and inadequate expiratory effort. In addition, regression studies indicated substantial divergence of the prediction coefficients and a higher degree of variability of the 1976 data compared with that found on subsequent testing. We know of no reversible restrictive pulmonary pathology that could account for these findings.

The principal and consistent respiratory finding in this work force exposed to PCBs was obstructive impairment which was found in approximately 15% of the

population. In the female subgroup we found a significant relation between exposure in the workplace and respiratory history and symptomatology in 1976. The serum PCB levels in females were 11% higher than in the males in 1976 and 50% higher in 1979. These elevated levels were related initially to the women's employment as capacitor sealers (solderers) and in salvage and repair, jobs with relatively high exposure levels, and subsequently perhaps to a diminished PCB metabolism compared with that of males. The association of serum PCB level and/or exposure and reduced FEV_1/FVC in females in 1976 appeared as an isolated finding, and no other correlation with spirometry in males or females was found.

The present study provided no compelling evidence that PCB exposure, as measured by exposure category or serum PCB levels, was correlated with the occurrence of persistent spirometric abnormalities. The restrictive impairments observed in 1976 were transient and were interpreted in terms of inadequate expiratory effort rather than pulmonary fibrosis. The past histories of respiratory illness and symptomatology, and the observed obstructive impairment by spirometry appear most likely to be coupled with heavy smoking, a complex of industrial exposures both prior to and during employment,¹¹ and rural upstate New York demographic factors.^{12,13} Our 1976 data, however, are suspect and this study serves to emphasize the importance of nurse/technician training in the conduct of spirometry.

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THE RELATION OF OCCUPATIONAL POLYCHLORINATED BIPHENYL
EXPOSURE TO CANCER AND TOTAL MORTALITY

PHILIP R. TAYLOR¹

JEANETTE M. STELMA²

IVAN AUGER²

CHARLES E. LAWRENCE²

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Footnote PageAbbreviations

1. CI = confidence interval
2. ln = natural logarithm
3. PCBs = polychlorinated biphenyls
4. ppb = parts per billion
5. SE = standard error
6. O = Obs = observed
7. E = Exp = expected
8. SMR = standardized mortality ratio
9. ICD = international classification of disease

¹Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, Blair Building, Room 6A01, Bethesda, Maryland 20892

(Reprint requests to Dr. Taylor)

²Statistical and Computer Science Laboratory, Wadsworth Center for Labs and Research, New York State Department of Health

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Running Head: Polychlorinated biphenyls and cancer.

Taylor, P.R. (National Cancer Institute, Bethesda, Maryland 20892), J.M. Stelma, I. Auger, and C.E. Lawrence. The relation of occupational polychlorinated biphenyl exposure to cancer and total mortality.

ABSTRACT

We studied the relation of polychlorinated biphenyls (PCBs) to total and cancer mortality in a cohort of men and women occupationally exposed to PCBs during the manufacture of capacitors. A total of 6292 employees who worked more than three months between 1946 and 1975 were followed for subsequent mortality through 1980 with identification of 136 cancer and 510 total deaths. The effect of PCB exposure was estimated in two ways: by comparing mortality rates for the entire cohort with national rates, and by comparing exposure in cancer deaths to that in matched reference subjects from within the cohort. For the internal comparison, cumulative PCB exposure, cumulative high-homolog serum PCB exposure, and average high-homolog serum PCB levels were estimated separately for each case and reference subject using an independently derived empirical model.

Results of this study indicate that overall cohort

mortality is significantly less than expected compared to the general populace (observed = 510, expected = 614.6; standardized mortality ratio [SMR] = 83, 95 per cent confidence interval [CI] = 76-90). Total cancer deaths do not vary from expectation (observed = 136, expected = 144.5; SMR = 94, 95 per cent CI = 79-111). None of the estimates of PCB exposure are associated with an increase in risk of total cancer, lung cancer (N=32 cases), or colorectal cancer (N=25 cases).

In summary, these data provide no evidence for an effect of high-homolog PCB exposure on cancer mortality, though the numbers of cancer deaths at individual sites are small.

INTRODUCTION

Polychlorinated biphenyls (PCBs) are chlorinated aromatic hydrocarbons consisting of mixtures of 210 different isomers having varying degrees of chlorination. First prepared in 1867, PCBs were commercially manufactured in the USA between 1929 and 1977. The chemical and thermal stability of PCBs resulted in their wide use in capacitors, transformers, hydraulic fluids, heat transfer fluids, lubricants, plasticizers, and as components of surface coatings and inks. Retention of these lipophilic compounds in animals, humans, and the general environment has been well documented and is related to both the degree of chlorination and the position of the chlorine atoms on the PCB molecule (1,2). The PCBs with lower degrees of chlorination (low homologs) tend to be more rapidly excreted while the more highly chlorinated PCBs (high homologs) are retained. Increasing concern about environmental contamination and potential health effects contributed to a ban in 1979 on the further distribution of PCBs in this country.

There have been a number of studies in animals which have found administration of various of the PCBs to result in tumor formation (3). The literature relating PCB exposure to cancer in humans is, however, much more

limited. A series of comparisons of fat sample analyses in cancer and noncancer patients conducted by Unger et al in Denmark found increased PCB levels in cancers at several sites, though results were inconsistent (4-6). Seven reports of cancer based on five different groups of occupationally exposed workers are found in the literature. Bahn et al. reported two melanomas from a group of 72 petrochemical workers exposed to PCBs in New Jersey when only 0.04 was expected (7). Roush found lung cancer in excess (7 observed, 2.7 expected) among 89 workers employed in the manufacture of PCBs in St. Louis (8). Excesses of liver (3 observed, 1.07 expected) and rectal (4 observed, 1.19 expected) cancer among capacitor manufacturing workers in two facilities located in upstate New York and western Massachusetts were noted by Brown and Jones (9). Follow-up of the same cohort seven years later continued to find an excess of cancer of the liver (5 observed, 1.9 expected) and rectal cancer (4 observed, 1.9 expected) (10). In Sweden, Gustavsson et al. found 21 total deaths among a cohort of 142 male workers engaged in the manufacture of capacitors when 22.1 were expected (11). Neither total cancer deaths (7 observed, 5.39 expected) nor incident cases (7 observed, 7.58 expected) were elevated. Most recently, Bertazzi et al. studied total and cancer mortality in Italian workers employed

in a capacitor manufacturing plant (12,13). An excess of total cancer among males was seen (14 observed, 5.5 expected), mainly at digestive, lung, and hematologic sites. Overall mortality in females exceeded expectation (34 observed, 25.8 expected) as did cancer mortality (12 observed, 7.7 expected).

We report here our study of cancer and total mortality among a large group of workers occupationally exposed to PCBs in the manufacture of capacitors.

METHODS

Description of the cohort

Between 1946 and 1977 two facilities of the same company located in upstate New York manufactured capacitors using PCBs with Aroclors 1254, 1242, and 1016 as their primary dielectric fluid. Our study population consists of the cohort of all employees who worked at either of these two facilities between the years 1946 and 1975 for a minimum of three months. Employees were first identified by personnel records for these years and later verified by obtaining copies of Social Security premium payment records for the years 1945 to 1965. A total of 6303 persons were verified in this way to have worked at least three months during the defined study period. Considering the Social Security premium reports as the reference, missing personnel records numbered only 41 after verification efforts were finished, indicating that the cohort was 99 per cent complete for 4129 persons who started work before 1965. A total of 11 additional exclusions were made for impossible dates ($n = 10$) or a missing date of birth ($n = 1$), leaving a final analytic cohort of 6292, including 2691 females and 3601 males.

Case ascertainment

Mortality was identified by searching a number of

sources. The primary resource used was the Social Security Administration premium payment report files (through 1980). This was supplemented by additional searches of the New York State Death files (through 1981), New York State Tumor Registry (through 1981), New York State Department of Motor Vehicles files (through 1982), company personnel records (through 1980), National Death Index files (for 1979 and 1980), and Veterans Administration records (for Vietnam deaths, through 1981). Records were considered complete through December 31, 1980 and this was used as the common closing date for all subjects in the study. Subjects with no indication of death after searching the above sources were assumed to be alive as of this date. Deaths known to have occurred after this date were not included in the analysis.

Exposure assessment

Work history information on the personnel records included a code, a description, and dates for each job at the facilities. The job descriptions in combination with manufacturing process information and industrial hygiene data were used to categorize all jobs into two broad exposure groups. Direct-exposure jobs were defined as those in which direct contact with PCBs occurred during the manufacturing process. These jobs were further characterized into subcategories as follows:

Low.....air contact only

Medium..air contact plus occasional dermal contact

High....air contact plus frequent dermal contact

All other jobs within the plants, including office and manufacturing areas where PCBs were not directly used, were termed indirect-exposure jobs. While PCBs were still in use at the facilities, environmental monitoring was performed in both direct- and indirect-exposure job areas during three industrial hygiene surveys. Results (summarized in Table 1) showed that in 1977, concentrations of PCBs in the indirect-exposure job areas were an order of magnitude below those in the direct-exposure job areas, although the indirect-exposure job areas had much higher PCB concentrations than did areas surrounding the plants, where values averaging 6.2 micrograms per cubic meter were recorded prior to discontinuation of PCB use. These concentrations all exceed previously reported urban ambient air averages of 0.1 microgram per cubic meter (14). Serum total PCB determinations performed on workers in these facilities (summarized in Table 2) demonstrated a geometric mean PCB concentration for workers in direct-exposure jobs more than four-fold higher than that in indirect-exposure jobs and almost 20-fold higher than that in non-exposed reference subjects. Exposure to chemicals at these facilities was limited to those used in the manufacture of

capacitors including PCBs, trichlorethylene, methyl isobutyl ketone, lead, zinc, tin, aluminum, iron, and epoxides (15,16). Exposure was homogeneous compared with the highly mixed exposure environment found in most chemical work environments.

Serum PCB levels and work histories were available for a sample of 194 employees at these plants. Linear regression methods were used on these data to develop a model for the prediction of high-homolog serum PCB levels. The resulting empirically derived model formed the basis for our primary index of high-homolog PCB exposure. This model is described in the Appendix. The model allowed us to estimate high-homolog serum PCB level in each cohort member at the time of each event being studied. Furthermore, through incorporation of different kinetic assumptions, the model can be used to estimate a number of different exposure parameters. For the present study, three different exposure estimates were made.

The first exposure estimate, cumulative exposure, is the sum of duration of employment times level of exposure across 5 levels and 4 eras of exposure. Algebraically it is summarized as:

$$CE_T = \text{cumulative exposure} = \sum_{t=0}^T E_t,$$

where T = year of diagnosis, and t = year of exposure.

The second exposure parameter is cumulative serum PCB level. Using first-order kinetic assumptions and a half-life determined empirically, this approach first estimates the serum PCB levels for each year beginning with initial employment and ending with the death of the case (for cases) or matched subject (for referent subjects), and then sums them up. This is expressed algebraically as:

CS_T = cumulative serum PCB level =

$$\beta + \sum_{x=0}^T S_x = \sum_{x=0}^T \sum_{t=0}^x E_t \exp(-k[x-t])$$

where T and t are as above, k = elimination constant, and S_x = serum level in year x .

The third exposure parameter used here is average annual serum PCB level. This measure is the estimated cumulative serum PCB level divided by the number of years since first employed and is expressed as:

S_T = average annual serum PCB level = CS_T

$\frac{\quad}{T+1}$

$$\frac{\sum_{x=0}^T \sum_{t=0}^X E_t \exp(-k[x-t])}{T+1}$$

Statistical methods

Two different analytic approaches were used in this study. The first estimated standardized mortality ratios (SMRs) to compare the observed mortality experience in the cohort with that which was expected based on national mortality. The second analysis was limited to cohort members only and compared estimated serum PCB levels in cases to those in reference subjects.

For the first analysis, the life table computer program of Monson was used (17). Person-years were combined into 5-year calendar time periods and 5-year age groups and multiplied by the corresponding U.S. white male (for male cohort members) and U.S. white female (for female cohort members) cause-specific mortality rates to yield the expected number of deaths. Observed and expected cause-specific deaths were compared using standardized mortality ratios (SMR, observed/expected x 100) with 95 per cent confidence intervals (CI) calculated using square root transformations of the Poisson variates. By convention, no CI was calculated when the difference between observed and expected deaths was less than 0.5, and no SMR or CI was calculated when no cases were observed or the expected

value was less than 1.0.

For the second analysis, a matched case-referent approach was used (18). Cancer deaths were identified and ordered by time since entry into the cohort. Matching by age (± 5 years of date of birth), sex, and time since initial employment at the capacitor manufacturing facility was used with selection of 10 reference subjects for each case. To simulate the risk set approach, reference subjects had to be alive (and therefore at risk of death) for at least as many years following initial entry into the cohort as the case to which they were matched. For one case only nine matches could be found, for another only eight could be found, and for a third only two were found. Selection of reference subjects was made with replacement so that a subject could serve as a reference for more than one case. In addition, reference subjects for early cases were eligible themselves to become cases later on. Each of the three PCB exposure estimates was calculated separately for each case and reference subject for the time period of initial employment until death of the case. Distributions for these estimates were skewed and ln-transformation was employed so that they more closely approximate normal. Computations for these analyses were conducted in SAS using PROC PHGLM with the blocking option to simulate a conditional logistic regression (19).

RESULTS

As of 31 December 1980, 5593 subjects in the cohort were known to be living, 510 were known to be dead, and 189 (3 per cent) were not known to be living or deceased. The number of deaths, years of employment, and person-years for the cohort are shown in Table 3. A total of 510 deaths including 136 cancer deaths were identified over 122,782 person-years of observation. Total mortality is significantly less than expected for males and females combined (observed = 510, expected = 614.6; SMR = 83, 95 per cent CI = 76-90) but cancer deaths are not different from expectation (observed = 136, expected = 144.5; SMR = 94, 95 per cent CI = 79-111). The observed and expected cause-specific mortality for males is shown in Table 4. The overall SMR ($355/429.9 \times 100 = 83$) is significantly less than 100, as is the SMR for all respiratory disease ($SMR = 10/21.6 \times 100 = 46$). No other significant deviations from expected are seen. Table 5 shows similar cause-specific mortality for females. The overall SMR ($155/184.6 \times 100 = 84$) is also significantly less than 100 for females. In addition, deaths from diseases of the circulatory system are less than expected ($SMR = 38/64.4 \times 100 = 59$) while deaths from accidents exceed expectation ($SMR = 21/11.0 \times 100 = 190$). No significant deviations

from expectation are seen for site-specific cancers in either males or females. The observed number of cases is slightly less than expected for males (69 versus 83.5) and slightly greater than expected for females (67 versus 60.9). Table 6 shows SMRs by latency intervals separately for males and females for cancer and total mortality. For longer latency periods, the cancer SMRs show a slight decrease for males and an increase for females. Tables 7 and 8 group cancers by systems and show, separately for males and females, the observed and expected numbers of cancer deaths adjusted for all-cancer mortality. This simple adjustment attempts to provide a more appropriate reference group for the occupational group being examined. Compared to unadjusted values, this approach results in SMRs for males that are slightly higher and for females that are slightly lower.

Table 9 presents characteristics of the subjects who are part of the matched case-referent study while Tables 10 - 12 show results of the conditional logistic analyses for all cancer mortality sites combined. Lung and colorectal cancer are also analyzed separately because they are the sites with the greatest numbers and are implicated based on a priori hypotheses. None of the three PCB exposure estimates is associated with an increased risk of cancer in the case-referent analyses. In fact, coefficients for

these exposure estimates for all-sites, lung, and colorectal cancer analyses are negative, indicating decreased risk with increased PCB exposure. Though inadequate numbers precluded more detailed analysis of the cancer sites previously mentioned in relation to PCB exposure (i.e., lung, colorectal, liver, melanoma, and lymph- and hematopoietic), calculated average serum PCB exposure is shown by case and reference status for the latter three sites in Figure 1.

DISCUSSION

We studied the relation of high-homolog PCB exposure to subsequent cancer mortality in a large group of men and women occupationally exposed during the manufacture of capacitors.

A total of 510 deaths were identified from among the 6292 cohort members after over 122,000 person-years of follow-up. Several features of this study plan and the findings make it unlikely that bias accounts for the results observed in this study. Persons were considered part of the cohort on the basis of personnel records originally obtained in 1975. Completeness of the records was confirmed using Social Security premium payment records for persons employed before 1965. Exposure was examined in two ways, both objective. First, all members of the cohort were considered exposed in comparison with the general population. And second, an additional analysis using only the cohort itself was conducted using an independently derived high-homolog serum PCB estimation model which relied on job code and date information obtained from the personnel records in conjunction with a separate assignment of exposure level (indirect, low, medium, high) to each job code. And finally, case ascertainment included a wide variety of resources and appears complete or nearly

complete for mortality. Though bias seems unlikely in this study, confounding could certainly be present. As is typical for occupational cohort studies, information on covariates is extremely limited.

There are a number of other limitations of the present study which bear mention. There is an acknowledged, inherent limitation in the interpretation of results from occupational cohort studies which compare the mortality of workers to that of the entire U.S. population. The "healthy worker effect" for total mortality typically observed in such studies is also seen in the present study. Data on the ideal reference group, a large external cohort with characteristics identical to those of the cohort under study but lacking PCB exposure, does not exist. The comparisons conducted within the cohort itself are limited because of the small numbers of site-specific cancers. Lung cancer deaths, for example, are the most common cause of death from cancer for both sexes combined but number only 32. We prefer to examine cancer incidence rather than mortality. However, we are unable to identify all incident cancers in persons who move out of New York state and are still alive. The consequence of this is a reduction in numbers of outcome events which is particularly acute for non-fatal cancers. And finally, a detailed, site-specific exposure evaluation is limited to

high-homolog PCB exposure.

There are a number of strengths that this study has in comparison with other studies of PCB-related mortality. First, this is the largest cohort of PCB-exposed workers in the U.S., and possibly in the world. As a result, this study has 2.2 times as many person-years of observation and cancer deaths, and approximately 1.7 times as many total deaths as the next largest reported study (10). Second, this is the only cohort study in which an attempt is made to quantify the level of individual exposure to PCBs. Studies based on the five different occupationally-exposed groups reported in the literature all assumed only that cohort members were exposed but do not rank or otherwise discriminate among their exposure levels. The present study includes both methods for classifying exposure. Finally, although the cancer site-specific analyses are limited to persons from within the plant, estimated PCB exposure includes both low and high values and varies widely among subjects. Model-derived estimates of average annual serum high-homolog PCB levels at the time of death, for example, range from 24 to 24,319 parts per billion.

In conclusion, we studied the relation of high-homolog PCB exposure to subsequent total and cancer mortality in an occupationally-exposed cohort. Total mortality was less than expected for both males and females. No effect of PCB

exposure on overall cancer rates was observed though there was a suggestion of an increase in rates with longer latency periods for females. Caution must be used in interpreting the results in light of the limited number of site-specific cancer deaths available for evaluation at this time. Follow-up of this cohort in future years will be possible and will give a more secure evaluation of the PCB hazard.

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TABLE III.1

Capacitor manufacturing plant PCB monitoring¹
 (geometric means, micrograms per cubic meter)

	Area Air Samples (October 1975)	Area Air Samples (April 1977)	Personal Air Samples ² (April 1977)
Direct Exposure	679	310	168
Areas	(n=30)	(n=16)	(n=31)
Indirect Exposure	260	27	
Areas	(n=1)	(n=16)	

¹Written personal communication, R. Lawton, 1980 (Note: caution should be used in making direct comparisons between results from 1975 and 1977 as the sampling techniques and analytic procedures employed in these 2 surveys were different)

²Time-weighted average

TABLE III.2
 Serum PCB concentrations in
 capacitor workers, 1979¹

	N	Geometric Mean (parts per billion)		
		Low homologs	High homologs	Total PCBs
Workers in Direct- Exposure Areas	147	269	33	302
Workers in Indirect- Exposure Areas	18	50	11	61
Reference Group ²	16	7	9	16

¹Written personal communication, R. Lawton, 1980.

²Employees without occupational PCB exposure working
 for the same company at another facility.

TABLE III.3
Characteristics of cohort and events by gender

	Males	Females	Total
Number of persons	3601	2691	6292
Number of deaths	355	155	510
Person-years	68505	54278	122783
Average age at entry	27	28	27
Average year of entry	1960	1960	1960
Average age at death	54	55	55
Average year of death	1970	1972	1971

TABLE III.4

Observed and expected deaths by cause for males

<u>ICD</u>	<u>Cause</u>	<u>Observed</u>	<u>Expected</u>	<u>SMR (95% CI)</u>
0	All causes of death	355	429.9	83 (74-92)
1	All malignant neoplasms	69	83.5	83 (64-105)
2	All infective & parasitic diseases	3	5.1	59 (12-151)
9	All tuberculosis	1	2.5	39 (1-216)
140-9	Cancer of buccal cavity & pharynx	2	2.6	75 (8-269)
150-9	Cancer of digestive organs & peritoneum	25	21.3	117 (76-173)
150	Cancer of esophagus	3	1.8	159 (32-463)
151	Cancer of stomach	1	3.7	26 (0-147)
153	Cancer of large intestine	9	6.9	130 (59-246)
154	Cancer of rectum	4	2.3	173 (47-444)
155-6	All cancer of liver	2	1.5	133 (15-480)
157	Cancer of pancreas	6	4.3	138 (50-301)
160-3	Cancer of respiratory system	20	29.0	69 (42-106)
161	Cancer of larynx	0	1.2	---
162	Cancer of lung	20	27.4	73 (44-112)

170	Cancer of bone
172-3	Cancer of skin
185	Cancer of prostate
186-7	Cancer of testis
188	Cancer of bladder
189	Cancer of kidney
190	Cancer of eye
191-2	Cancer of brain & nervous system
193	Cancer of thyroid
200-9	All lymph- & hematopoietic cancer
200	Lympho- & reticulosarcoma
201	Hodgkin's disease
204-7	Leukemia & aleukemia
202-3, 208	Cancer of other lymphatic tissue
210-39	Benign neoplasms
240	Allergic, endocrine, metabolic, & nutritional diseases
250	Diabetes mellitus

1	0.4	---
2	2.0	98 (11-355)
4	3.6	110 (30-281)
1	0.9	---
0	1.9	---
4	2.1	184 (49-470)
1	0.0	---
1	3.3	30 (0-165)
0	0.1	---
6	9.6	62 (23-136)
0	2.0	---
0	1.6	---
4	3.7	106 (29-272)
2	2.1	94 (11-339)
0	1.3	---
5	7.0	71 (23-165)
4	5.8	69 (18-176)

280-9	All diseases of blood & blood-forming organs
290-317	Mental, psychoneurotic, & personality disorders
320-89	All diseases of nervous system & sense organs
390-458	All diseases of circulatory system
393-8	Chronic rheumatic heart disease
410-4	Arteriosclerotic heart disease
430-8	All vascular lesions of CNS
460-519	All respiratory diseases
480-6	All pneumonia
492	Emphysema
493	Asthma
520-77	All diseases of digestive system
531-3	All gastric & duodenal ulcer
571	Cirrhosis of liver
580-629	All diseases of genito-urinary system

1	0.9	---
3	3.2	92 (19-269)
3	4.4	68 (14-199)
164	190.9	86 (73-100)
4	4.5	89 (24-227)
126	137.1	92 (77-109)
14	21.3	66 (36-110)
10	21.6	46 (22-85)
4	7.5	53 (14-135)
3	5.0	60 (12-174)
0	0.7	---
16	23.2	68 (39-111)
2	2.6	76 (8-273)
10	13.6	73 (35-135)
3	5.0	59 (12-173)

582 Chronic nephritis

680-709 All diseases of skin

710-38 All diseases of bones

780-99 Symptoms, senility, & ill-defined
 conditions

800-998 All external causes of death

800-949 All accidents

810-27 Motor vehicle accidents

950-9 Suicide

1	2.0	49 (1-275)
0	0.2	---
1	0.7	---
5	5.5	91 (29-212)
72	75.2	96 (75-120)
56	50.8	110 (83-143)
22	27.2	81 (51-122)
10	16.1	62 (30-114)

TABLE III.5

Observed and expected deaths by cause for females

<u>ICD</u>	<u>Cause</u>	<u>Observed</u>	<u>Expected</u>	<u>SMR (95% CI)</u>
0	All causes of death	155	184.6	84 (71-98)
1	All malignant neoplasms	67	60.9	110 (85-140)
2	All infective and parasitic disease	0	2.6	---
9	All tuberculosis	0	1.0	---
140-9	Cancer of buccal cavity & pharynx	2	0.8	---
150-9	Cancer of digestive organs & peritoneum	19	12.4	152 (92-238)
150	Cancer of esophagus	0	0.4	---
151	Cancer of stomach	2	1.5	125 (14-453)
153	Cancer of large intestine	9	5.4	165 (75-313)
154	Cancer of rectum	3	1.2	235 (47-686)
155-6	All cancer of liver	1	1.1	90 (1-500)
157	Cancer of pancreas	4	2.1	182 (49-466)
160-3	Cancer of respiratory system	12	7.1	167 (86-292)

161	Cancer of larynx
162	All cancer of lung
170	Cancer of bone
172-3	Cancer of skin
174	Cancer of breast
180-4	Cancer of all genital organs
180-2	Cancer of all uterus
180	Cancer of cervix uteri
181-2	Cancer of corpus uteri
183-4	Cancer of other genital organs
188	Cancer of bladder
189	Cancer of kidney
190	Cancer of eye
191-2	Cancer of brain & nervous system
193	Cancer of thyroid
200-9	All lymph- & hematopoietic cancer
200	Lymph- and reticulosarcoma
201	Hodgkin's disease

0	0.1	---
12	7.4	160 (83-280)
0	0.2	---
1	1.0	---
13	15.4	84 (45-144)
13	10.5	123 (65-210)
7	5.6	125 (50-257)
5	3.5	140 (45-326)
2	1.8	108 (12-391)
6	4.9	122 (44-265)
1	0.4	---
1	0.8	---
0	0.0	---
0	1.9	---
0	0.1	---
4	5.3	75 (20-193)
0	1.1	---
0	0.7	---

204-7	Leukemia & aleukemia
202-3,208	Cancer of other lymphatic tissue
210-39	Benign neoplasms
240-79	Allergic, endocrine, metabolic & nutritional diseases
250	Diabetes
280-9	All diseases of blood & blood-forming organs
290-317	Mental, psychoneurotic, & personality disorders
320-389	All diseases of nervous system & sense organs
390-458	All diseases of circulatory system
393-8	Chronic rheumatic heart disease
410-3	Arteriosclerotic heart disease
430-8	All vascular lesions of CNS
460-519	All respiratory diseases
480-6	All pneumonia

3	2.0	144 (29-421)
1	1.2	79 (1-440)
0	1.1	---
4	5.2	76 (20-194)
4	4.2	94 (25-240)
1	0.7	---
1	0.9	---
2	2.7	72 (8-259)
38	64.4	59 (42-81)
2	3.9	51 (6-184)
23	34.5	67 (42-100)
9	13.4	67 (30-127)
7	8.0	87 (35-180)
3	3.2	92 (18-180)

492	Emphysema
493	Asthma
520-77	All diseases of digestive system
531-3	All gastric & duodenal ulcer
571	Cirrhosis of liver
580-629	All diseases of genito-urinary system
582	Chronic nephritis
680-709	All diseases of skin & cellular tissue
710-38	All diseases of bones
780-99	Symptoms, senility, & other ill-defined conditions
800-998	All external causes of death
800-949	All accidents
810-27	Motor vehicle accidents
950-9	Suicide

0	1.0	---
2	0.6	---
6	10.6	57 (21-123)
0	0.7	---
3	5.9	50 (10-146)
2	3.1	64 (7-232)
2	1.0	190 (21-686)
0	0.3	---
1	0.9	---
0	2.1	---
26	18.2	142 (93-209)
21	11.0	190 (117-290)
8	6.3	126 (54-248)
4	5.1	77 (21-198)

TABLE III.6

Standardized mortality ratios (and number of cases) for cancer
and total mortality by years since starting work and sex

Cancer Mortality	Years Since Starting Work			
	<u>0-9</u>	<u>10-19</u>	<u>20+</u>	<u>Total</u>
Males	92 (13)	83 (23)	78 (33)	83 (69)
Females	63 (8)	115 (23)	126 (36)	110 (67)
Total	78 (21)	97 (46)	97 (69)	94 (136)
Total Mortality				
Males	77 (80)	85 (123)	84 (152)	83 (355)
Females	67 (28)	81 (47)	94 (80)	84 (155)
Total	74 (108)	84 (170)	87 (232)	83 (510)

TABLE III.7

Observed and expected cancer deaths adjusted¹
for all-cancer mortality (males)

<u>Site (ICD)</u>	<u>Observed</u>	<u>Expected</u>	<u>SMR²</u>	Adjusted	Adjusted
				<u>Expected</u>	<u>SMR (95% CI³)</u>
All cancers (140-209)	69	83.5	83	69.0	100 (---)
Gastrointestinal (140-57)	27	24.0	112	19.9	135 (89-191)
Respiratory (160-3)	20	29.0	69	24.0	83 (50-123)
Genitourinary (180-9)	9	8.7	103	7.2	124 (56-220)
Lymph- and Hematopoietic	6	9.6	62	7.9	75 (27-148)

(200-9)					
Other	5	6.1	81	5.0	98 (31-206)
(170,172-3,					
190,191-2,193)					

¹Expected values are adjusted by multiplying them by the O/E for all-cancer mortality (0.83).

²SMR = standardized mortality ratio = observed/expected x 100.

³CI = confidence interval.

TABLE III.8

Observed and expected cancer deaths adjusted¹
for all-cancer mortality (females)

<u>Site (ICD)</u>	<u>Observed</u>	<u>Expected</u>	<u>SMR²</u>	Adjusted	Adjusted
				<u>Expected</u>	<u>SMR (95% CI³)</u>
All cancers (140-209)	67	60.9	110	67.0	100 (---)
Gastrointestinal (140-57)	21	13.3	157	14.6	143 (88-211)
Respiratory (160-2)	12	7.4	160	8.1	147 (76-243)
Genitourinary (180-9)	15	11.9	126	13.0	114 (64-181)
Lymph- and Hematopoietic (200-9)	4	5.3	75	5.8	68 (17-153)
Other (170, 172-3, 174,	14	18.8	74	20.6	67 (37-108)

190,191-2,193)

¹Expected values are adjusted by multiplying them by the O/E for all-cancer mortality (1.10).

²SMR = standardized mortality ratio = observed/expected x 100.

³CI = confidence interval.

TABLE III.9

Characteristics of subjects from matched case-referent study

Median (range)

	All Subjects		Lung Cancer		Colorectal Cancer	
	Cases (N=135) ¹	Referents (N=1339)	Cases (N=32)	Referents (N=318)	Cases (N=25)	Referents (N=249)
Age at death (years) ²	56 (21-84)	54 (20-84)	58 (38-84)	58 (28-84)	56 (36-78)	54 (26-81)
Sex (% male)	50%	50%	62%	62%	52%	52%
Duration exposure (years) ³	20 (1-32)	20 (1-32)	19 (5-30)	19 (5-30)	22 (2-32)	22 (2-32)
First employed (year)	1951 (1946-72)	1950 (1946-71)	1951 (1946-70)	1951 (1946-70)	1951 (1946-65)	1949 (1946-70)

Cumulative

PCB	2482	2826	2987	2897	1612	3084
exposure ^{3,4}	(24-57656)	(24-85559)	(43-44469)	(24-83421)	(115-57656)	(24-62782)
(ppb x years)						

Cumulative

serum PCB	11389	14048	15794	15063	8310	15953
exposure ^{3,4}	(98-301659)	(74-436911)	(218-232345)	(226-436911)	(328-301659)	(74-326375)
(ppb x years)						

Average

serum PCB	613	749	709	799	455	820
(ppb) ^{3,4}	(24-12066)	(24-24319)	(34-8605)	(24-24319)	(60-12066)	(24-17478)

¹One case in the SMR analysis is deleted from the case-referent analysis

because of lack of adequate information to calculate exposure level.

²For referents, age at time of death of matched case.

³Prior to death (cases) or prior to death of matched subject (referents).

⁴See methods for detailed description of exposure calculation.

TABLE III.10

Relation of ln of estimated cumulative PCB exposure level to cancer mortality from conditional logistic regression model

Site	Number	Coefficient ¹	SE ²	95% CI ³	P-value
All	135	-0.1116	0.0620	-0.2331, 0.0099	0.072
Lung ⁴	32	-0.1150	0.1261	-0.3621, 0.1321	0.361
Colorectum ⁵	25	-0.0216	0.1391	-0.2942, 0.2509	0.876

¹ln odds ratio per unit increase in cumulative PCB exposure.

²Standard error.

³Confidence interval.

⁴ICD 160-3

⁵ICD 153-4

TABLE III.11

Relation of ln of estimated cumulative serum PCB exposure level to cancer mortality from conditional logistic regression model

Site	Number	Coefficient ¹	SE ²	95% CI ³	P-value
All	135	-0.1406	0.0686	-0.2750, -0.0061	0.058
Lung ⁴	32	-0.1261	0.1389	-0.3983, 0.1461	0.364
Colorectum ⁵	25	-0.0509	0.1521	-0.3490, 0.2472	0.737

¹ln odds ratio per unit increase in cumulative PCB exposure.

²Standard error.

³Confidence interval.

⁴ICD 160-3

⁵ICD 153-4

TABLE III.12

Relation of ln of estimated average annual high-homolog PCB level to cancer mortality from conditional logistic regression model

Site	Number	Coefficient ¹	SE ²	95% CI ³	P-value
All	135	-0.1298	0.0695	-0.2660, 0.0064	0.061
Lung ⁴	32	-0.1238	0.1415	-0.4011, 0.1534	0.381
Colorectal ⁵	25	-0.0334	0.1541	-0.3354, 0.2686	0.828

¹Ln odds ratio per unit increase in cumulative PCB exposure.

²Standard error.

³Confidence interval.

⁴ICD 160-3

⁵ICD 153-4

APPENDIX

A regression model approach was used to develop a high-homolog serum PCB estimation model based on data from a company survey. The survey collected blood from 194 persons including 152 males and 42 females in 1976 selected to include all current employees whose job required direct PCB contact in high air level zones, employees in the immediate periphery of the high-exposure zone, and employees having high but intermittent exposure. A follow-up survey was conducted in 1979 on all of the 194 directly exposed workers who were still available, numbering 174. Because of our interest in PCBs that are retained in the body longer, we focused our efforts on a model for high-homolog PCBs (Aroclor 1254). Because of concern over a systematic laboratory error in the 1976 data, only values from 1979 were used in this analysis. Complete job history records through 1976 and serum Aroclor 1254 measurements from 1979 were available on 157 employees.

While additional information was gathered on these 157 persons, information used in development of the prediction model was limited to items found in the company personnel records and the job exposure categorization (described earlier under Methods). This was done to allow us to generalize use of the model to the entire cohort of 6292

persons. Work history variables included the number of months at jobs from each of four exposure levels (described in the text under Methods) for each of four time intervals. In 1954 the use of highly-chlorinated Aroclor 1254 was phased out and replaced by Aroclor 1242; in 1965 major engineering changes occurred, including closed process filling of capacitors and improvements in ventilation, which presumably resulted in substantial reduction in exposure to PCBs; and in 1971 Aroclor 1242 use was stopped in favor of Aroclor 1016. To account for the potential influence of these changes, separate variables corresponding to the periods 1946-54, 1955-65, 1966-71, and 1972-76 were incorporated into the model to indicate the era of exposure:

Era 1.....1946-54 (25-33 years before sampling)

Era 2.....1955-65 (14-24 years before sampling)

Era 3.....1966-71 (8-13 years before sampling)

Era 4.....1972-76 (3-7 years before sampling)

Weighting of the independent variables was employed to satisfy the regression assumptions of homoscedasticity, normal error distribution, and linearity.

The model assumes first order kinetics. With an estimated half-life of 3.32 years determined empirically by application of simple linear regression to the difference in serum PCB estimates from 1979 and 1983 on a subset of

150 persons in this cohort, serum PCB level can be estimated at any point in time. When the half-life is set to infinity, cumulative PCB exposure up to the time of interest is estimated.

Indicator variables for exposure levels by time intervals were created using data from all 157 persons. Running the full least squares regression model with 16 exposure-time categories, ten influential outlier values (standardized residual ≤ -2.5 or ≥ 2.5) were identified, reviewed, and removed. Removal of the ten outliers resulted in an improvement in the R^2 from 0.56 to 0.71. The model was then simplified by removal of all four of the statistically insignificant variables from era 4 and a single insignificant variable for low exposure during era. The final, reduced model was:

$$\begin{aligned}
 \text{Serum PCB} = & 24.7 \\
 & + 75.3 \times (\text{No. months at indirect in era 1}) \\
 & + 652.1 \times (\text{No. months at low in era 1}) \\
 & + 882.7 \times (\text{No. months at medium in era 1}) \\
 & + 77.5 \times (\text{No. months at high in era 1}) \\
 & + 6.6 \times (\text{No. months at indirect in era 2}) \\
 & + 39.4 \times (\text{No. months at medium in era 2}) \\
 & + 95.8 \times (\text{No. months at high in era 2}) \\
 & + 1.7 \times (\text{No. months at indirect in era 3}) \\
 & + 0.7 \times (\text{No. months at low in era 3})
 \end{aligned}$$

$$\begin{aligned} &+ 7.3 \times (\text{No. months at medium in era 3}) \\ &+ 16.0 \times (\text{No. months at high in era 3}) \end{aligned}$$

Regression coefficients are equal to serum PCB concentration per era-specific exposure category month. The R^2 for this reduced model was 0.69 based on 147 observations.

LN OF AVERAGE ESTIMATED SERUM PCB VS. CANCER SITE

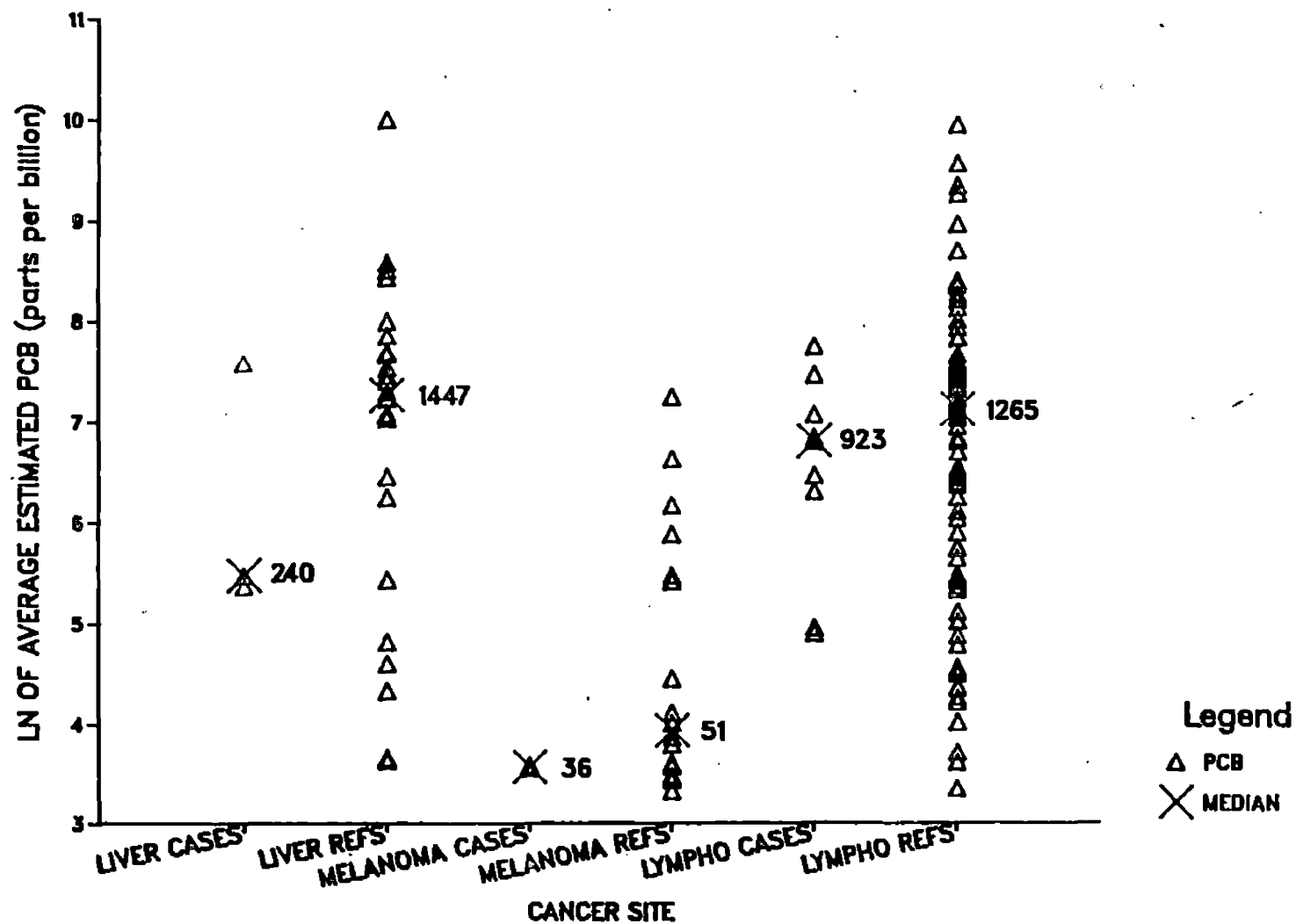


Figure III.1

FIGURE III.1 - LEGEND

Estimated serum PCB level is shown for only two cases of melanoma. The one additional skin cancer found in the SMR analysis lacked adequate information to calculate exposure.