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HUMAN HEALTH EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBs) AND POLYBROMINATED BIPHENYLS (PBBs)[1]

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INTRODUCTION

Polychlorinated biphenyls (PCBs) are chemical compounds with the empirical formula $C_{12}H_{10-n}Cl_n$, with n = 1–10. They are a mixture of chlorinated biphenyl congeners. Theoretically, 209 such congeners are possible, but at least 20 congeners have never been identified in commercial products. In addition, PCBs may contain polychlorinated dibenzofurans and chlorinated quaterphenyls as impurities. PCBs were discovered before the turn of the century, and the useful industrial properties of mixtures obtained by chlorination of biphenyl were recognized early. In 1966 the discovery of PCBs in environmental samples (1) spurred renewed interest in the analysis and toxicity of these compounds.

In recent years many industrial nations have taken steps to control the flow of PCBs into the environment. PCBs and PCB-containing formulations are restricted (an exception is sometimes made for mono- and dichloro-PCB) for most uses, except for categories such as closed-system electrical equipment and hydraulic fluids in mining equipment.

Commercial production of PCBs began in the United States in the late 1920s. In 1971, Monsanto Chemical Company voluntarily stopped open-ended uses of PCBs, and subsequently only the lower chlorinated biphenyls

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were produced (Aroclor 1242 and 1016). In 1977 the company ceased production entirely (2). Many PCBs manufactured in the past (3) are still in use in old transformers, but even this use is decreasing. The estimated cumulative production and consumption of PCBs in the United States in the period 1930-1975 (in millions of pounds) was as follows: total production, 1400; imports, 3; domestic sales, 1253; exports, 150.

PCBs are inert chemicals that are fairly resistant to degradation. Because of their stability and lipophilicity, they have accumulated in the environment and in organisms. They have been identified in indoor air (4) at concentrations of 0.1 $\mu g/m^3$ (5), in fish (6, 7) and other food products, and in sediments from lakes and rivers (8, 9). PCBs have also been identified at varying concentrations in soil (0.01 mg/kg–100 mg/kg) (10). They do not occur naturally. Thus, their presence in the environment is linked with human activities, and concentrations are higher in urban and heavily industrialized areas than in rural and remote areas. However, trace amounts are also found in remote areas, since the air may transport such chemicals over large distances.

Although PCBs are no longer used commercially in the United States because of their persistence? they are still present in our environment. A number of transformers and capacitors that contain PCBs, however, are still in use. Results of laboratory experiments showed that pyrolysis of PCBs at temperatures of 200-600°C could result in the formation of significant amounts of the more toxic polychlorinated dibenzofurans (PCDFs) (11).

In February 1981, an electrical fire occurred in a New York State office building in Binghamton, N.Y. The fire, which originated in a switch gear in the basement, caused the bushings to crack on a nearby transformer. About 180 gallons of PCB dielectric fluid Pyralon (65% Aroclor 1254, 35% chlorinated benzenes and trace additives) were lost. A fine layer of oily soot covered many of the internal surfaces of the 18 floors of the building. Analysis of a soot sample showed that it contained various isomers of chlorinated dibenzofurans, 2,3,7,8-tetrachlorodibenzodioxin, other chlorinated dibenzodioxins, and chlorinated biphenylenes. Some of these chemicals are much more toxic than the PCBs. Because of these findings the Binghamton state office building was closed, and workers wearing respirators and protective clothing began an extensive cleanup of the building. The cleanup operations lasted four years, and the cost has been enormous (12). Since then several other transformer fires have occurred. These fires have not resulted in as much contamination as the one in Binghamton, partly because the transformers in the other fires were usually located in a separate vault (13).

The problems with polybrominated biphenyls (PBBs), which are also a mixture of chemicals, have been quite different. In 1970 a chemical company in Michigan manufactured polybrominated biphenyls as flame retardants. The same company also produced magnesium oxide, a chemical commonly mixed

into feed for livestock. The flame retardant was called Firemaster and the magnesium oxide, Nutrimaster. In 1973 some bags of Firemaster were accidentally sold as Nutrimaster and mixed into animal feed. This resulted in widespread contamination in the state of Michigan (14). Since 1974 PBBs have not been produced in the United States. At the time of the exposure little was known about the toxic effects of PBBs. Ten years after the Michigan residents were exposed, no clinical illness has been causally linked to PBB exposure in this group, although chloracne was apparently noted in some workers who manufactured PBB.

HUMAN EXPOSURE

Because PCBs are ubiquitous and very persistent in the environment, humans have been and will continue to be exposed to them, particularly in industrialized countries. PCBs may be inhaled in small amounts through the air or ingested through food. In the United States today, people are primarily exposed to PCBs by consuming fish from contaminated waters (9). In the past, some farm families were exposed to PCBs from dairy products; these PCBs originated from coating material used in the inside of silos (15). In addition, workers who repair transformers and workers who handle toxic wastes may also be exposed (16).

The PCB products that were manufactured by Monsanto in the United States had the trade name "Aroclor." The particular kind of Aroclor is identified by a four-digit number. The first two digits refer to the 12 carbon atoms, and the second two refer to the percent, by weight, of chlorine in the mixture. Thus, Aroclor 1254 contains about 54% chlorine, and Aroclor 1260, about 60% chlorine.

The composition of this mixture of chemicals, with different properties, changes once it gets into the environment and into organisms. Some components of the mixture are more easily degraded in the environment than others. As a result the PCBs identified in the environment resemble Aroclor 1254 but are not identical to it. Similarly, the PCB mixtures found in humans usually resemble Aroclor 1254 if exposure occurred primarily through the environment. A different composition of the PCBs may be found in serum or adipose tissue samples from occupationally exposed workers. For instance, if the workers are primarily exposed to Aroclor 1016 or Aroclor 1242, which contain much less of the more highly chlorinated homologs, then their gas-chromatographic patterns resemble a combination of Aroclor 1016 or 1242 and Aroclor 1254. For this reason Smith et al (17), in evaluating occupational exposure, divided PCBs into high and low chlorinated biphenyls. The gas-chromatographic pattern of the PCB mixture present in humans can be used to determine whether the exposure occurred primarily

through occupation or through the environment, or, in the case of occupational situations, whether most of the exposure was recent or occurred many years ago.

Although 93% of the US population eats fish, the average annual per capita consumption is small: 15 lbs. per year (6, 7). If PCBs are to be quantitated in fish, the edible portion rather than the whole fish must be examined. Because of their lipophilicity, PCBs are preferentially stored in the hepatopancreas of the fish, giving erroneously high levels if the whole fish is analyzed. Similarly, levels in cooked fish are lower (6).

Generally, PBBs are not found in the environment because they have had less commercial use than PCBs. PBB contamination is essentially restricted to Michigan's lower peninsula. Most persons who lived in Michigan during the 1973–1974 period have low-level PBB body burdens (18). The greatest degree of contamination occurred mainly in areas with contaminated farms; this segment of the population still has appreciable body burdens (19).

Since PBBs and PCBs are lipophilic, they are preferentially stored in adipose tissue. They are also present, to a smaller extent, in serum and other organs and in human milk. The concentration of these materials in different organs depends upon the lipid content of such organs, with the exception of the brain where the concentration is lower than the lipid content would indicate. PCBs and PBBs pass the placenta and are primarily excreted through bile and milk. In addition to lipid content, the ratios between adipose tissue, blood, and vital organs are influenced by exposure level, sex, age, length of exposure, and also by whether exposure is current. At very low concentrations an analytical imprecision influences the ratios much more than at higher concentrations (19). Since human milk is relatively easy to obtain, it has been used to monitor human exposure. Jensen (20) recently summarized results of such monitoring studies. Average levels of PCBs below 2 ppm (mg/kg) in milk fat have normally been found, although women living in heavily industrialized urban areas may have higher levels. The fat concentration in human milk averages 2.6–4.5% (21). At 2% fat, 1 liter (l) of milk would contain 0.04 mg or 40 μg if the PCBs were present in milk fat at a concentration of 1 ppm. If an infant weighed 5 kg and imbibed 750 ml of milk per day, it would take in about 6 μg/kg, a dose that exceeds the 1.5 μg/kg dose calculated as acceptable by Cordle et al (6). At 1% milk fat this dose would be reduced to 3 μg/kg. As the infant gains weight, the dose on a kilogram body weight basis will be reduced to some extent, however; milk is the sole food source for only about six months. After the first week, the daily milk intake is estimated to be 150 ml/kg body weight per day. This consumption gradually falls after two months and declines to 120 ml/kg body weight at four-to-six months. Finally, the amount of PCBs and other halogenated organic chemicals declines with time. However, at low concentrations this

may not be obvious because of continued exposure of the mother and the variability of the analytical results. In addition to PCBs, human milk contains trace amounts of many other persistent chemicals. Whether the infant's consumption of such chemicals has any adverse health effects is not known.

Most persons, particularly in industrialized countries, have had some exposure to polychlorinated biphenyls even if they do not eat fish. The concentrations at which such exposure presents a risk are not clear. Recently, Cordle et al (6, 7) calculated the dose of PCBs to people consuming fish from Lake Michigan. They concluded that persons eating Lake Michigan fish ingested an average of 46.5 mg of PCBs per year; this amount ranged from 14.17 to 114.31 mg/year/person. The calculated mean daily dose received by the exposed group was 1.7 μg/kg/day and ranged from 0.09 to 3.94 μg/kg/day. Thus, the average sports fisherman consuming contaminated fish would receive a total PCB dose equal to 200 mg in about 4.3 years. No adverse health effects or groups of symptoms clearly related to PCB exposure could be identified in this exposed group. The presence of PCBs in the exposed persons has not caused any observable adverse health effects similar to those observed in the Yusho population (see below). However, this finding does not exclude the possibility that the effects are too subtle for detection or that they require long-term observation.

Similarly, in Michigan an analysis of 1,075 human milk samples showed that all contained PCB residues and that the residues ranged from trace amounts to 5 ppm (mg/kg) based on fat level. The public health significance of PCB residues in human breast milk and their effects on breast-fed infants are unclear. Since there are no human data on which to base public health policy, risk predictions for PCBs have been based on results from animal studies, particularly the positive bioassay studies. Reviewing these data, Cordle et al (6, 7) concluded that a 2-ppm (mg/kg) tolerance for PCB in fish be established, since a 1-ppm (mg/kg) tolerance does not greatly reduce the estimated risk.

As previously mentioned, some of the isomers of the PCBs and PBBs are much more easily degraded or metabolized. Because they can be metabolized, they are more easily excreted. Others may be retained in the body for long periods; in general, the PBBs appear to be more persistent in human tissues than the PCBs (19, 22).

POLYCHLORINATED BIPHENYLS

Background

When PCBs were first used industrially some workers developed chloracne. Results of early animal studies seemed to suggest that PCBs might have some toxic effects on the liver. Beyond that observation no information was avail-

able. Because PCBs were so inert chemically, they were not considered to cause a great deal of toxicity. In 1968 a poisoning outbreak occurred in Japan (23) that affected over 1,000 persons. These individuals had purchased rice oil, in large drums, from a single source and had used this rice oil for cooking. Chloracne was one of the leading signs in those who became ill. It was soon discovered that PCBs had been used as a heat-exchange fluid in the factory where the rice oil originated. PCBs had leaked out of the columns in which they were contained into the rice oil when the rice oil was heated. Since the disease was caused by ingesting contaminated rice oil, it was called Yusho (rice-oil disease). When the outbreak first occurred, its association with exposure to PCBs was not clear. At that time the capabilities for measuring these types of chemicals in tissues and body fluids were limited, particularly in Japan. Therefore, early in the investigation total chlorine, rather than PCBs, was measured. Retrospectively determining the precise dose these patients received is difficult. Whether the consumed oil was uniformly contaminated is also not clear. However, a relationship between the amount of rice oil ingested and some symptoms could be established (24). Because of this poisoning outbreak and other environmental problems, animal studies were started in Japan, in the United States, and in other countries to elucidate the toxic effects of PCBs. These data are summarized in several detailed reviews (16, 25, 26).

Animal Studies

This article addresses primarily the human health effects of PCBs and PBBs. Therefore we highlight only recent results from animal studies that might give a better understanding of implemented public health policies and potential human health effects. One of the difficulties in using animal data to predict human health effects for PCBs and related compounds is that animal species vary greatly in their responses. Further, many of the animal studies use relatively high doses. Therefore, determining how such animal studies relate to the human situation is difficult. Some animal species, such as the subhuman primates, the guinea pig, and the mink, are much more sensitive to the toxic effects of PCBs than the rat or the mouse; also the types of toxic effects and morphological changes in the organs of different species vary.

Most animal studies conducted during the 1970s used mixtures of PCBs. In general, PCBs were found to affect reproduction and the immune response, and to cause liver tumors in rodents (16). When different mixtures of PCBs were studied, however, the results were inconsistent. For instance, the mixture Aroclor 1254 affects reproduction in rats at much lower doses than does Aroclor 1260 (27).

More recently some of the isomers of the PCB mixture were found to be much more toxic than others (28–32). The more toxic isomers constitute only

a very small portion of the mixture, particularly those with less chlorine by weight, such as Aroclor 1242 or Aroclor 1016. Recently, Schaeffer et al (33) found that a German PCB mixture—Clophen A-30, with an average composition of 1% monochlorobiphenyl, 20.7% dichlorobiphenyl, 57.4% trichlorobiphenyl, 17.3% tetrachlorobiphenyl, 1.8% pentachlorobiphenyl, 1.0% hexachlorobiphenyl, 0.6% heptachlorobiphenyl, and 0.1% octachlorobiphenyl—produced a 3% incidence of hepatocellular carcinoma, whereas Clophen A-60 produced a 61% incidence of hepatocellular carcinoma in Wistar rats. The incidence of the disease in the controls was 2%. The Clophen A-60 had an average composition of 0.2% monochlorobiphenyl, 1.1% dichlorobiphenyl, 2.2% trichlorobiphenyl, 3.1% tetrachlorobiphenyl, 19.8% pentachlorobiphenyl, 43.2% hexachlorobiphenyl, 25.3% heptachlorobiphenyl, 4.7% octachlorobiphenyl, and 0.3% nonachlorobiphenyl. Similarly, Norback & Weltman (34) and Kimbrough et al (35) were able to produce hepatocellular carcinomas in rats with Aroclor 1260, the more highly chlorinated Monsanto product.

When Aroclor 1254 was fed to rats, fewer liver tumors developed in exposed rats (36); however, the incidence of gastric intestinal metaplasia and adenocarcinoma of the stomach increased (37, 38). Whether PCB fractions without hexachlorobiphenyls, heptachlorobiphenyls, and octachlorobiphenyls produce hepatocellular carcinomas in rodents should be explored.

Particularly in the United States, mixtures such as Aroclor 1242, 1254, and 1016 were used more than Aroclor 1260. Because of these differences in potency, the PCBs in heavily contaminated areas of our environment should be characterized according to their isomeric composition. For instance, whether the PCBs in Lake Michigan are of the same composition as those found in New Bedford Harbor, Massachusetts, is not clear.

Aside from tumor formation, PCBs cause a variety of other biological effects, such as the induction of enzymes (39). In some species they may cause atrophy of the thymus, intrahepatic bile duct hyperplasia, hyperplasia of the epithelial lining of the urinary bladder, atrophy of the sebaceous glands, and hyperkeratosis of the ducts (40). Some isomers are fetotoxic, and some produce metaplasia of the sebaceous glands, nailbeds, ameloblasts, thymus corpuscles, and gastric mucosa (28, 41). Subhuman primates, mink, and guinea pigs are particularly sensitive to the toxic effects of PCBs; other species, such as the rat, the mouse, and the dog, can tolerate much higher doses. From empirical observations, humans also appear to be less sensitive to the toxic effects of PCBs. The ability to store these chemicals in adipose tissue may be protective. Generally, the subhuman primates and mink have less adipose tissue than humans. Animals with greater ability to store vitamin A on a quantitative basis, such as the hamster and the rat, are somewhat less susceptible to the toxic effects of these types of compounds (42). The

mechanism by which these types of chemicals affect hepatic retinoids is not clear. Apparently, the duration of the reduction of hepatic retinoids does not correlate with the induced aryl hydrocarbon hydroxylase (AHH) activity (43).

Body Burdens

Many investigators have reported PCBs in human tissues (44, 45). In the United States, according to data from the Centers for Disease Control (CDC), mean PCB serum levels are about 5–7 ng/ml (ppb), although some patients may have higher serum levels without any documented unusual exposure. These data were also summarized by Kreiss (46). Levels in adipose tissue and in human milk fat are 100–200 times as high, since PCBs are highly lipid soluble (20). Mes et al (47) reported that PCB levels in adipose tissue of accident victims ranged from 0.9–9.4 mg/kg.

Sahl et al (48) surveyed PCB blood levels in 738 pre-employed and 1,058 currently employed workers of a utility company. The median blood level before employment was 4 mg/l and the range, 1–37 mg/l. These levels were quite similar to those in the currently employed group.

Patients who died of cancer in Denmark had somewhat higher levels of PCBs in their adipose tissue (49). Since terminal cancer patients have usually lost a great deal of weight, bioconcentration may have occurred. Similarly, in patients with highly impaired liver function, tissue concentrations of xenobiotics may be slightly higher than those in healthy persons. However, levels remained higher if parameters such as weight, height, occupation, and residence were considered (50), whereas levels of PCBs in breast fat tissue from patients with breast cancer were similar to those of controls (51).

Furthermore, Lawton et al (52) demonstrated that random errors and interlaboratory variations in procedure and methods of data reporting can influence serum and adipose PCB levels. Unless an interlaboratory quality-control system is set up, measured levels between laboratories are not necessarily comparable. For instance, Lawton et al (52) found that the results of repeated analyses on serum samples of known composition showed the 95% prediction interval for an individual measurement to be about ± 42%. This interval depends on the method of extraction, the procedure used, and the means of quantitation.

Summary of Human Epidemiology Studies

Recently, investigators studied the predominantly black population of Triana, a small rural town in the southern United States (53). This population was excessively exposed to DDT residues by consuming contaminated fish. The residents also had PCB body burdens. Fish consumption correlated positively with PCB blood levels; no other source of PCB exposure could be established. These researchers noted that PCB serum levels increased with age and that

levels were lower in females of each age group. Similar findings were m for DDT residues. The serum cholesterol level was positively associated w the log PCB level, independent of age, sex, fish consumption, body-m index, and alcohol consumption. Rates of borderline and definite hypert sion for study participants were 30% higher than those expected on the b of national rates (54). Log PCB serum values contributed significantly explaining the variability of log systolic and diastolic blood pressure multiple regression analysis (55). Median total cholesterol levels of dividuals in the United States increase with age from about 150 to 160 mg at age 20 to over 200 mg/dl at age 50. PCBs in blood are influenced by ser lipid content, and populations with inherently lower total serum choleste levels appear to have a different PCB serum to adipose tissue ratio. T age-associated increase in blood PCB levels could be related to the lo half-life of some PCB isomers that are preferentially retained in mamm (29); as long as exposure continues, a true steady state between intake a excretion is never reached. Other variables affecting body burdens may differences in metabolism with age. In the Triana studies, the blood levels total DDT residues also increased with age, and others have made simi observations (56, 57). Lawton et al (58) studied workers who had be exposed to electrical-grade Aroclor 1016, 1242, and/or 1254; the stu covered the period from before the workers were exposed to two years af PCB exposure ceased. Serum levels for the lower chlorinated PCBs in 19 ranged from 57–2270 ppb and in 1979, from 12–392 ppb; for the high chlorinated PCBs serum levels ranged from 6–142 ppb in 1977 and fr 4–108 ppb in 1979. These findings again illustrate the preferential excreti of lower chlorinated PCB. Lawton et al (58) also found that cholesterol lev correlated with log serum PCBs. Similar associations with log serum PC were found for log gamma glutamyl transpeptidase (GGTP) and, in so cases, for log alanine aminotransferase. When the PCB concentrations we expressed as levels in serum lipids, all the associations between serum lipi or enzymes and log serum PCBs disappeared except for those between l GGTP and log PCBs. Similarly, Chase et al (59) found no significa correlation between either serum triglycerides or aminotransferases and t PCB levels in adipose tissue. How age and length of exposure affect the parameters is not adequately explained in the article. Finally, Akagi Okumura (60) were not able to confirm a positive association between PC blood levels and elevated blood pressure in Yusho patients.

Thus, as Brown (61) has suggested, the positive association between PC serum levels and elevated triglycerides and serum cholesterol can be e plained by the increased solubility of PCB in serum with higher lipid conten

In several cross-sectional studies of exposed workers, only min abnormalities not necessarily related to PCB exposure have been detecte

(62-66). In cross-sectional studies, however, the ability to evaluate chronic health effects is limited. In several studies, a positive association between results of one liver function test—the test for γ-glutamyltranspeptidase—and PCB blood levels has been found. Kimbrough (67) has summarized earlier studies on the health effects of PCBs observed in workers.

In 1930 and 1940, chloracne, a disfiguring skin disease, was reported among workers exposed to PCBs. One of the clinical features of chloracne is the chloracne cyst, which is skin colored and measures from 1–10 mm in diameter, with a central opening. The other dominant lesion is the comedo. The skin lesions may only involve the face, but many also extend to other parts of the body. Microscopic examination of human skin biopsies from chloracne cases shows markedly dilated hair follicles filled with keratin. The sebaceous glands involute partially or completely. The epithelial cells lining the hair follicles and the adjacent surface epithelium proliferate, and acanthosis is present. In old lesions, the epithelial lining of the greatly dilated hair follicles becomes atrophic.

Jones & Alden (68) examined 17 of 23 workers engaged in the production of PCBs. The workers had chloracne involving the face, genitalia, trunk, and extremities. Before the outbreak of chloracne in the plant, the electrical property of the PCBs had fallen below specifications, and the color had deepened. In the report, symptoms of illness were extensively described for the first worker who was diagnosed as having chloracne. This worker complained of lassitude, loss of appetite, and loss of libido. Over the years, other cases of chloracne following exposure to PCBs have been reported. Most of these involved exposure to vapors that developed when PCBs were heated (69).

At times, the skin rashes that developed in workers were accompanied by pruritus. Some workers also complained of burning of the eyes, nose, and throat; dry throat; nausea; and dizziness. Meigs et al (70) reported chloracne in workers who had been exposed to PCB vapors for 5–14 months. The concentration of PCBs in the workers' breathing zone was 0.1 mg/m^3. Evidence of slight liver injury was also present. Ouw et al (71) found air levels in a capacitor plant that ranged from 0.32–1.44 mg/m^3 Aroclor 1242 (PCB). Here workers complained of burning eyes, face, and skin in general, and persistent body odor. One worker suffered from chloracne, five complained of eczematous rashes, and a few had abnormal liver function tests. These workers had a mean PCB blood level of about 400 ppb (μg/kg). In most studies of workers with chloracne, evidence of liver injury was also found; in one study, workers who did not have chloracne were found to have abnormal liver function (69).

PCBs also affect the liver by inducing mixed-function oxidases. Alvares et

al (72) determined that in five workers occupationally exposed to Aroclor 1016—a PCB mixture primarily composed of dichlorobiphenyls, trichlorobiphenyls, tetrachlorobiphenyls, and pentachlorobiphenyls—plasma antipyrine half-life was significantly lower than that in matched controls, suggesting the induction of mixed-function oxidases in the liver. These workers had been exposed to Aroclor 1016 for at least two years and had no obvious symptoms of PCB poisoning.

Other health effects are eye and upper respiratory irritation. Warshaw et al (65) studied a group of 326 workers in a capacitor plant with a mean employment of more than 15 years and mean employee ages of 41.1 years for males and 47.3 years for females. Work-related eye or upper respiratory irritation was reported by 48% of the workers, and 10% had experienced tightness in the chest. Spirometric studies were conducted on 309 workers; 66 of them were dropped from the study because they had been exposed to talc, textile dust, or asbestos. Thus, 243 men were available for analysis. In males, there were about twice as many smokers and exsmokers as nonsmokers. In females, the proportion of nonsmokers was higher. Thirty-four of the workers (14%) had a reduced vital capacity, and 27 of these demonstrated a restrictive pattern of impairment. Because of additional variables such as smoking and asbestos exposure, these findings are difficult to interpret.

Taylor et al (73), in an attempt to determine whether the fetus would be affected in capacitor workers, examined pregnancy outcome and birth weight, and found that the gestation period was reduced by one week. The infants weighed slightly less than the controls; this finding could be explained by the reduced gestation period. Smoking and alcohol consumption were not controlled, however; furthermore, whether the socioeconomic status of this group of women was similar to that of the control group is not clear. Thus, until other studies confirm these findings, they should be viewed with caution.

In several papers Jacobson and his associates reported behavioral changes and a reduced gestation period in association with higher fish intake or higher intake of PCBs (9, 74–76). Furthermore, Jacobson et al (74) reported that intrauterine PCB exposure may have a delayed effect on central nervous system functioning. Since genetic makeup, the mother's lifestyle, and acute illness also affect these parameters, these findings are difficult to interpret. Furthermore, many other chemicals are also excreted in human milk (20). Rogan & Gladen (77), for instance, found that mothers with high levels of DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] in their milk tended to wean their infants earlier, as they did not thrive. Apparently, PCB levels in milk were higher in older women, women who drank alcohol regularly, and primiparas (78).

Whether high levels of DDE affect lactation is not clear. In animals, DDT

homologs, but not specifically DDE, have been shown to have estrogenic effects (79). Before these findings can be clarified, additional studies must be done.

No conclusive evidence thus far reported shows that occupational exposure to PCBs causes an increased incidence of cancer. Bahn et al (80) reported results of a preliminary study of a group of 51 research and development employees and 41 refinery plant employees at a New Jersey petrochemical facility. Between 1949 and 1957 these workers had been exposed to Aroclor 1254. Three melanomas and two carcinomas of the pancreas were found. This incidence was significantly higher than expected. Exposure to other chemicals also occurred, however, and the cohort was small.

Brown & Jones (81) conducted a retrospective mortality study of 2,567 workers in two capacitor plants. The relatively few deaths (163) severely limited the statistical power of the study, and the average follow-up was only 15 years, whereas latency periods of 20–30 years are not uncommon for cancer. Over 50% of the sample had exposure to PCBs for two years or less. Deaths from liver cancer, cirrhosis of the liver, and rectal cancer were slightly higher than expected, but not significantly for both sites combined. The observed increase for cancer of the rectum was statistically significant among females at one of the plants. In a follow up study (82) no additional cancers of the rectum were noted, and the standardized mortality ratio (SMR) dropped from 336 to 211. However, two additional cancers of the liver and biliary tract were observed, bringing the total of these tumors to five as reported on the death certificates. However, a review of the medical records raises questions about at least one of these tumors.

Bertazzi et al (83) reviewed the mortality of 290 males and 1,020 females who had worked for six months or more in capacitor production. Males had a statistically significant increased number of deaths from all neoplasms. When deaths were analyzed by organ system, deaths from neoplasms of the digestive system, the peritoneum, and the lymphatic and hematopoietic tissues were higher. Among females, all causes of deaths were significantly elevated. The actual numbers in this study, however, were small.

Yusho and Yucheng

Two outbreaks of poisoning have been reported that followed the ingestion of rice oil contaminated with polychlorinated dibenzofurans, biphenyls, and quaterphenyls (PCQs). The first outbreak occurred in Japan in the summer of 1968 and the second outbreak, in Taiwan in 1979. Ironically, the outbreak in Taiwan repeated what had occurred 10 years earlier in Japan. Many studies of these two outbreaks have been published in Japanese or Chinese. In 1984 some of the information in these reports was published in English in the

American Journal of Industrial Medicine 5:1–153; the information is also summarized in volumes 59 and 60 of *Environmental Health Perspectives*.

In Japan and Taiwan the disease was first recognized because chloracne developed in the affected patients (84). In Japan, members of all of the affected households had purchased rice oil from a specific company, and the toxic rice oil produced or shipped on February 5 and 6 of 1968 contained large amounts of Kanechlor 400, a brand of PCB with a chlorine content of 48%. At the time of the outbreak, no analytical methods specific for PCBs were available in Japan; the concentration of Kanechlor 400 in the oil was therefore estimated from the organic chlorine content to be 2,000–3,000 ppm. Kanechlor 400 had been used for heating the rice oil in a metal container at over 200°C, at a reduced pressure of 3–44 mm Hg, to remove odorous material from it. Kanechlor (K) must have leaked from the heating pipe into the processed oil, but the actual mechanism of the contamination has apparently not been determined. The reanalysis of the K-rice oil, once the methods were developed, showed that some of the oil samples contained 1,000 ppm (mg/kg) PCB. This concentration was much lower than had originally been estimated. Therefore, other chlorine-containing compounds were assumed to be in the oil, and additional samples were analyzed. The oil was found to contain an average of 5-ppm polychlorinated dibenzofurans (85). According to Buser et al (86), the Yusho oil contained more than 40 polychlorinated dibenzofuran isomers, including the highly toxic 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 2,3,4,7,8-pentachlorodibenzofuran (PCDF). In addition, the oil contained PCQs at a concentration of 866 ppm (87, 88).

According to estimates made by Kuratsune (89), the total amount of PCB, PCDF, and PCQs consumed by the patients was, on the average, 633 mg of PCB, 3.4 mg of PCDF, and 596 mg of PCQ. This calculates to roughly 157 μg/kg body weight/d. PCB, 0.9 μg/kg body weight/d. PCDF, and 148 μg/kg body weight/d. PCQ. At this dose the length of the latent period between exposure and onset of clinical illness was roughly 71 days, with a range from 20 to 190 days. Some of the oil the patients consumed may have contained higher or lower levels because in such situations contamination is usually not uniform. Furthermore, the patients consumed different amounts of contaminated rice oil. The severity of symptoms was positively associated with the amount of contaminated rice oil consumed (24).

Early in the outbreak the patients had chloracne, dark-brown pigmentation of the nails, itching, pigmentation of the skin, swelling of the limbs, pigmented mucous membranes, eye discharge, hyperemic conjunctivae, jaundice, swelling of the upper eyelids, a feeling of weakness, numbness of the limbs, and fever. Over 1,000 people were affected. Thirty-six babies showed fetal PCB syndrome, which consists primarily of a dark-brown pigmentation

of the skin (Cola babies). The cutaneous pigmentation was caused by an increase in melanin pigment in the epidermis (90). The mucous membranes were also pigmented. In all cases, the pigmentation disappeared by the time the babies were between two and five months old. In affected infants, the face was edematous, and spotty calcifications were noticed in the parietal and occipital areas of the skull. In a few of the infants, the teeth had erupted at birth. Subsequently, the adult patients with clinical disease complained of having to expectorate a great deal and, on auscultation, wheezing was noted; however, on examination, there was no evidence of bronchial asthma or pulmonary emphysema. In many of these patients, the respiratory symptoms have persisted, and the patients have chronically infected airways. In the early 1970s, some changes were noted in the patients' serum immunoglobulin levels, but the levels returned to normal. Over time the severity and the extent of the skin lesions improved considerably in the exposed population. Fifteen years after the accident, only a very few patients had extensive chloracne (91).

About five years after the outbreak of Yusho, tissue and body fluids of Yusho patients were analyzed for various congeners of PCB and PCDF. At this time, the PCB levels in adipose tissue were 1.9 ± 1.4 ppm (mg/kg). In the liver they were 0.08 ± 0.06 ppm and in blood, 6.7 ± 5.3 ppb (μg/kg); thus, they were not very different from levels in the general population in Japan. On the other hand, the isomeric distribution for the PCBs in the Yusho patients varied from that in the control population in the same area (92). About 40 PCDF congeners were identified in the rice oil that the Yusho patients ingested. Only some PCDF congeners were retained in the body for a long time; they included 2,3,6,8-TCDF, 2,3,7,8-TCDF, 1,2,4,7,8-PCDF, 2,3,4,7,8-PCDF, and 1,2,3,4,7,8-hexachlorinated dibenzofurans. Since these congeners do not have free adjacent carbon atoms, they are not as easily metabolized and excreted. More of the 2,3,4,7,8-PCDF than the other isomers was retained in the patients' tissues. In the five patients studied, the concentration of this isomer ranged from 6.9 ppb (μg/kg) in a specimen obtained in 1969 to 0.1 ppb (μg/kg) in a specimen collected in 1977. Measurable concentrations of TCDFs were only detected in the earlier years. Although not the most toxic isomer, the 2,3,4,7,8-PCDF caused mixed-function oxidase induction at a dose of 1 μg/kg in rats, and atrophy of the thymus, suggesting toxicity at a very low dosage level. Thus, the clinical manifestations observed in these patients were primarily caused by the PCDFs, specifically by the more toxic isomers.

In the Yucheng episode, it was never determined with certainty how the rice oil was contaminated (93). In 1979 a school for blind persons informed a local health bureau in Taichung County that a strange disease characterized by an acnelike skin eruption had been occurring frequently among students and

staff since the end of March. At the same time, 85 of 150 workers in a r plastic shoe factory had the same symptoms. Later that year, this ou was also reported to a local health bureau. Victims in both outbreak consumed the same brand of cooking rice oil, which had been manufa by the same company and which had been purchased in the same stor this reason the rice oil was the prime suspect in the outbreak. In add reports of outbreaks in other companies and in the general populatic victims had consumed the same type of C-rice oil.

Finally, because the disease resembled the Yusho disease in Japan, sa of C-rice oil and patients' blood were analyzed in Japan and were fo contain either a Kanechlor-400 or a Kanechlor-500 mixture at concentr as high as 65 and 108 ppm (mg/kg), respectively. Over 2,000 patients finally identified as having been poisoned by contaminated rice oi samples collected from other outbreaks contained PCBs at concentrati 31–300 ppm (mg/kg). Retrospective studies determined that the peri PCB intake ranged from 3 to 9 months. The average total intake for person varied from 0.77 to 1.8 mg of PCB. Within the first year o outbreak, the blood levels of PCB in 13 patients ranged from 3 ppb to ppb. Most of the patients had blood levels between 11 and 150 ppb (μ The symptoms observed in these patients were quite similar to those al described for the patients in the 1968 Yusho outbreak in Japan.

The rice oil was not only contaminated with PCBs but also with PCDF polychlorinated quaterphenyls. It contained the same major compone PCDFs observed in the rice oil in Japan—namely, 2,3,4,6,7-PCDF 2,3,4,7,8-PCDF. Relatively high concentrations of 2,3,4,5,3',4'-hexa robiphenyl were found in the blood and adipose tissue of the Yu patients. This particular PCB isomer is biologically quite active, an concentration of 2,3,4,3'4'-pentachlorobiphenyl was also elevated in patients. Furthermore, as in the Yusho patients, the concentration of 2,3 TCDF was comparatively low (92). Chen et al (94) analyzed addi samples of the oil, blood, and adipose tissue of the Yucheng patients. investigators identified several TCDF and PCDF isomers. Appar 2,3,7,8-TCDF was only a minor component in the oil; the major comp was 2,3,4,8-TCDF. One of the major furans in the toxic oil was 2,3,4 PCDF.

The concentrations of the PCDFs in different oil samples ranged from to 1.68 ppm. Polychlorinated quaterphenyls were present in concentra ranging from 25 to 53 ppm (mg/kg). Overall, the concentrations of P and PCQs were lower in these oil samples than in the oil samples tha caused the Yusho outbreak. Whether these oil samples were representat not really known. The 3,4,3'4'-tetrachlorobiphenyl was also identified i oil that caused Yucheng disease in Taiwan. This isomer is considered

the most toxic PCB isomer present in commercial PCB preparations (95); it was present at a concentration of about 1%. Most other commercial PCB preparations, such as the Aroclors, in the United States have not been shown to contain this particular isomer.

In addition to the epidemiological studies, some disease-specific investigations were also conducted. The blood pressure of the Yucheng and Yusho patients was not affected (60). Although some of the patients in the Yusho cohort have died of cancer (90), the number has been small; because the latency period may be long, the population should be followed for a longer period to determine whether the cancer incidence will increase.

Although PCBs and related compounds are known to affect reproduction in animals, and although they affected some fetuses and neonates in the Yusho and Yucheng episodes, the information on reproduction and fetal toxicity in general is very limited. In one such study, Hara (96) examined women working in a capacitor plant who also nursed their infants and who themselves had mild chloracne and erythema of the skin. The human milk of some of these women contained, on a whole milk basis, PCB levels that ranged from below 50 ppb (μg/kg) to about 400 ppb (μg/kg). Forty children of these mothers were followed for a five-year period. Some children were found to have "decayed" nails, gingival pigmentation, mottled enamel, and dental caries. No relationships between these changes or symptoms to PCB blood levels, however, were observed. The general population in the United States and other countries also has body burdens of PCBs, PCDFs, and polychlorinated dibenzodioxins (97, 98). However, these background concentrations—particularly for the biologically active isomers—are far lower than they were in the Yusho and Yucheng patients, even several years after exposure.

Chang et al (99) examined the delayed immune response in 30 Yucheng patients and compared their responses with those of 50 controls. The mean age of patients in both groups was about 14 years. The authors injected a solution of streptokinase and streptodornase subcutaneously into the flexor side of the forearm. The response was read at 24 hours (hr) and again at 48 hr after injection. Eighty percent of the controls had an induration of 5 mm or more in diameter 24 or 48 hr after they were injected; only 43% of the exposed group responded similarly. All of the poisoned patients had dermal lesions, and the percentage of patients with a positive response decreased with increasing severity of the skin lesions (chloracne). Furthermore, the degree of the dermal lesions appeared to be associated with the whole blood PCB concentrations. Patients with minor skin lesions that were classified as grade 1 appeared to have a normal skin response. The same authors found that PCBs caused a decreased concentration of IgA and IgM, but not of IgG, in serum.

Furthermore, the percentages of total T cells, active T cells, and T mu cells decreased, whereas the percentage of B cells and T gamma cells were not

affected (100). These two reports are the first in which the effect on th immune response was actually correlated with body burdens of PCBs and i which only severely poisoned patients showed this effect. This finding i consistent with the findings from animal studies in which relatively high dose of PCBs affected the immune response and also caused some other adverse effects.

In the Japanese and the Taiwanese Yusho and Yucheng poisoning out breaks, sensory neuropathy was reported in a number of patients for whon nerve conduction velocities were measured (101, 102). The blood levels o the various chemicals (PCBs, PCDFs, PCQs) were negatively correlated wit the lowered nerve conduction velocity, suggesting that these types of chemi cals affect nerve conduction velocity. (It is not quite clear why most in vestigators measure nerve conduction velocity to detect sensory neuropathy Other tests that would measure the detection of vibration, touch, and tempera ture would be more useful from a clinical perspective.)

Seppalainen et al (103) examined 16 men working in a cardboard plant wh were exposed to fumes that resulted from the explosion of 15 capacitor containing Clophen A-30. The first PCB air concentrations, measured 5.5 h after the explosion, were 8,000 to 16,000 $\mu g/m^3$ air. PCDFs were als formed. The soot samples contained tetrachlorodibenzofuran up to 90 $\mu g/g$ of which 6.5 $\mu g/g$ was 2,3,7,8-tetrachlorodibenzofuran. In addition, mono chloropyrenes and dichloropyrenes were found. Most of the men had t transient sensory neuropathy in their lower extremities.

Chang et al (104) reported increased urinary δ-aminolevulinic acid uropor phyrin excretion in 69 Yucheng patients over that of 20 controls. No informa tion on the patients' clinical conditions or on how these findings related t degree of exposure was given. No such observations have been reported from Japan.

POLYBROMINATED DIPHENYLS

Since the toxicity of PBBs both in laboratory animals and livestock wa recently reviewed (105), we do not review it here in detail. In laboratory animals, PBBs generally cause effects similar to those that the PCBs cause. They produce morphological changes in the liver, affect reproduction, and promote biochemical changes, such as hepatic porphyria and induction of mixed-function oxidases. Teratogenic effects have also been noted. In addition, atrophy of the thymus has been reported, and hepatocellular carcinomas have been produced in both rats and mice. The overall findings reported in animal studies are similar to those that have been reported for PCBs.

Although the PCB contamination of the environment is a more general problem, the PBB contamination primarily affects certain areas within the state of Michigan. Most persons living within the lower peninsula of Michi-

gan have had slight exposure, since the contamination resulted from dairy products and since normal marketing channels for these products involved the mixing of milk from many producers in relatively few processing facilities. In addition, most cull dairy cattle are used for hamburgers and processed meat products that would also receive wide distribution. Thus, the marketing system diluted the degree of exposure for the individual; however, it increased the number of those exposed. In 1978, the distribution of PBBs was comprehensively studied in a probability sample of 1,738 persons. PBB levels in serum were determined, and 844 adipose tissue samples were also analyzed for PBBs. PBBs were detected in 97.3% of the adipose tissue samples, in 68% of the adult serum samples, and in 72.7% of the serum samples from children. The mean PBB concentration in adipose tissue was 400 ppb (μg/kg); in serum it was 1.3 ppb (μg/kg) for adults and 1.8 ppb (μ/gkg) for children. The highest adipose tissue concentration was 37 ppm (mg/kg) (18). In additional studies, when cohorts of PBB-exposed residents of Michigan were compared with residents of the state of Wisconsin, a higher prevalence of a variety of symptoms and complaints was noted in the Michigan residents (106). Similarly, in comparative neurobehavioral studies, the Michigan population was found to be affected more than that in Wisconsin (107).

Since the findings were not correlated with body burdens of PBB in any of these studies, determining whether other factors may be responsible for these differences is difficult. In 1976, the Michigan Department of Public Health established a cohort of farmers who had been exposed to varying concentrations of PBBs in their products and their environment. A total of 3,877 persons were enrolled. They included farm residents, direct recipients of farm products, chemical workers and their families, and a few persons who had been originally studied in a smaller previous study.

The serum PBB levels in this entire group ranged from no detectable levels to 1,900 ppb (μg/l), with a mean of 21.2 ppb (μg/l) and a median of 3 ppb (μg/l). Because of the wide range of exposure and because results could be analyzed by regression analyses with exposure as a variable, a comparison group for acute health effects was not included. This cohort was found to have various symptoms and conditions; however, these symptoms did not correlate with PBB body burdens. Symptom prevalence rates were slightly higher in persons with no detectable PBBs in serum than in those with measurable quantities. In all groups, including chemical workers and quarantined farm residents, the highest prevalence rates were in persons with the lowest serum PBB levels (22).

Similarly, in this study and in a previous immunologic study (108) no dose-related depression of lymphocyte function in persons exposed to PBBs could be demonstrated. All these findings suggest that there may be no causal

relationship between the abnormal lymphocyte functions observed in some persons or the prevalence of other symptoms and exposure to PBBs. This cohort of Michigan residents is still being followed by the Michigan Department of Health in collaboration with the Centers for Disease Control. Several studies of subgroups of this population and surveys for chronic health effects have been conducted since the cohort was first assembled (109, 19). When serum and adipose tissue concentrations were compared, a significant correlation was found. The serum:adipose tissue concentration ratios ranged from 1 to 140 to 1 to 260 for pregnant women and male chemical workers, respectively. Males from farms had a significantly different ratio of 1 to 325 to 329. Potential transplacental passage of PBBs was demonstrated, since they could also be found in the fetus and newborn. Cord blood contained one-tenth of the concentration found in the maternal serum, which indicated partial placental passage. Human milk contained PBBs at 107–119 times the quantity found in maternal serum. PBBs were also detected in bile and feces, which indicates that these materials can be transferred into the intestinal tract. All of these concentrations were measured long after the population had first been exposed to PBBs (19). Concentrations of PBBs observed in bile and feces were about one half to seven-tenths of the serum levels and are probably about 0.5% of the adipose tissue levels. These findings indicate that PBBs are very slowly excreted, which is consistent with the findings of Tuey & Matthews in rats (110). The estimated half-life for PBB is 6.5 years.

More recently, two groups of Michigan residents—those with high PBB serum levels and those with PBB serum levels around 1 ppb—were matched for age, sex, and smoking. For both groups, various clinical laboratory tests were conducted, blood pressure was measured, and height and weight were determined. In this study, 83 participants had PBB serum levels of 50 ppb ($\mu g/l$) or more. In the middle group, 83 had PBB levels of 5–49 ppb and 96 had PBB levels of 0–44 ppb ($\mu g/l$) in serum. Urinary porphyrins were also measured in all of the participants. Thus far, the final results of this study have not been reported. For most of the parameters studied—which included serum glucose, triglycerides, high-density lipoproteins, various liver functions, creatinine, uric acid, thyroid function, proteins, calcium and phosphorus in serum, and also measurement of various porphyrins—no differences of clinical significance were found among different groups (M. Barone, personal communication). (Note: Even though significantly more women in the high PBB group used birth-control pills than women in the low PBB group, too few were using them to affect urine porphyrin levels.) In none of a variety of other studies conducted on this population as well as other groups in Michigan did any findings indicate that exposure to PBB had impaired the health of the exposed group. All of these studies have been reviewed by Fries (105).

Although this population was exposed during a 9-month period in 1973 and 1974, whether it will have chronic health effects is unknown. This particular cohort needs to be followed for 30 to 40 years before the question of chronic health effects can be intelligently addressed. Two problems with assessing chronic health effects are that the cohort, in spite of its size, is still relatively small and that the amount of exposure it has received varied widely. Although some members of the group exposed to PBBs have relatively high body burdens, these burdens are still appreciably lower than those of rats in which liver cancer developed.

In the study by Kimbrough et al (111), liver cancer developed in the rats that received a dose of 1,000 mg/kg body weight. This dose for humans would roughly translate into a dose of 70 grams per person. These amounts are much greater than the estimated mean total exposure per person. The highest exposure was about 11.7 grams, and the mean was 170 mg per person. In rats given 200 mg/kg, a dose that for humans would be between 12 and 14 grams, only neoplastic nodules developed in their livers; there was no evidence of hepatocellular carcinomas. Of course, whether humans would be more or less susceptible to the toxic effects of PBBs and whether their response would be similar to that of rats is not known.

In conclusion, various toxic effects of PBBs and PCBs have been described in laboratory animals. In humans, acute poisoning outbreaks have only occurred following exposure to a combination of PCBs and PCDFs. When humans were exposed only to PCBs or PBBs, the only observed acute effects have generally been minor. So far, no significant chronic health effects have been causally associated with exposure to PCBs or PBBs.

Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the US Department of Health and Human Services.

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Feature Article

Polychlorinated Biphenyls: How Do They Affect Human Health?

Until 1971, polychlorinated biphenyls (PCBs) were used commercially in the U.S. in capacitors and transformers, carbonless copying paper, paints, and hydraulic fluid. While many countries have since restricted PCB use, the compounds are still found in old transformers, capacitors, and other products.

PCBs are a group of 209 stable, fat-soluble chemicals. Not easily broken down, they have accumulated in fish from polluted waterways, in wildlife, and in human organs, fatty tissue, blood, and milk. In the late 1960s and early '70s, PCBs were also detected in meat, eggs, milk, and cereal. Today, however, because of regulatory restrictions and other measures, polluted fish are the primary food source of PCBs for humans.

Because they are fat soluble, PCBs tend to concentrate in fatty tissue, and to a great extent, PCB levels in different organs depend on the organs' fat content. Thus, in humans, fatty tissues contain the highest PCB concentrations. In fish, the highest levels are found in body fat and the hepato-pancreas, not the edible portion.

Aroclor is the commercial name for the American product of PCB mixtures. Different mixtures are further identified by codes, such as 1242, 1016, 1254, that designate the percent of chlorination of the mixture. Because the time necessary for different components of PCB mixtures to break down in the environment varies, PCB mixtures found in soils, sediments, and biota have a different composition from commercial products. Most are similar, but not identical to Aroclor 1254.

Studies in laboratory animals

To learn how PCBs might affect health, investigators have studied PCB exposure experimentally in animals and in humans occupationally or accidentally exposed to the compounds.

Except for feeding studies in mink, which used PCB-polluted fish, most animal studies have tested commercial products. Results show that the toxicity of commercial mixtures varies. Mixtures like Aroclor 1260, with a high degree of chlorination, produce liver cancer in rats. Mixtures with much less chlorination, on the other hand, yield a much lower cancer incidence, with a tumor incidence similar to that in unexposed rats. Most tests have not demonstrated any mutagenic properties for PCBs.

Other adverse effects observed in different animal species vary. While all mixtures and congeners* tested induce mixed-function oxidases in the liver, the type of enzymes induced varies. PCB isomers that appear more toxic and that are retained longer in the body seem to induce aryl hydrocarbon hydroxylase. Liver enlargement seems to accompany enzyme induction. In some species fed high doses of PCBs, investigators have observed liver cell necrosis and fat accumulation in liver cells.

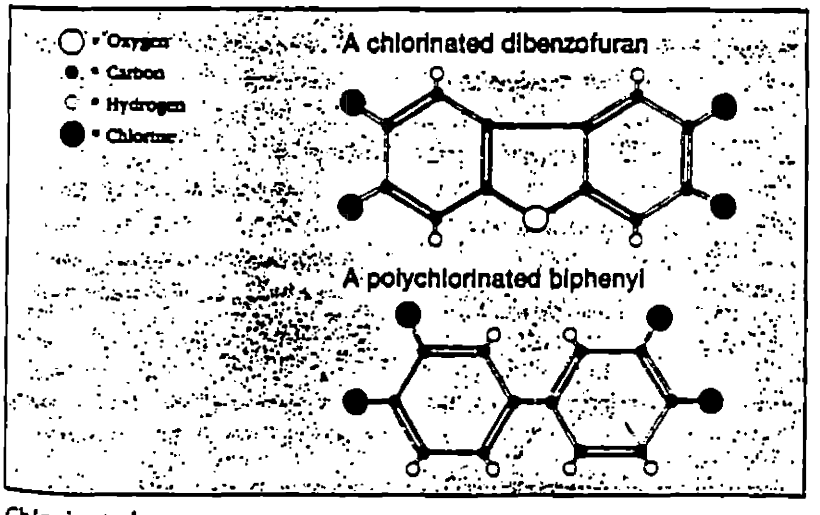
by Renate D. Kimbrough, M.D. U.S. Environmental Protection Agency, Office of Regional Operations, Director, Health & Risk Capabilities

Rhesus monkeys exposed to technical PCBs have developed hyperplasia, or overgrowth, of the epithelium of the gastric mucosa. In rats, investigators have observed cell transformation, noting that hepatic cells transformed into pancreatic cells. This effect on cell differentiation, apparently modified by the epithelial growth factor, is more pronounced in rats exposed to Aroclor 1254. Because the mixtures tested may have been contaminated with chlorinated dibenzofurans, such contamination may have contributed to the toxic effects and be partly responsible for the variation in effects seen between mixtures and between animal species.

In experimental animals, some mixtures affect reproduction more than others, but all effects have been fetotoxic. In minks and monkeys, investigators have noted spontaneous abortions; in rodents, they have seen resorptions. Exposure to lower doses may reduce the weight of the offspring. No one has reported malformations after exposure to PCBs. Finally, some species, such as monkey and mink, are much more susceptible to the toxic effects of these chemicals than rats or mice.[1,2,3]

Effects on human health

Thus far, no conclusive adverse effects have been demonstrated in people who carry body burdens of PCBs from environmental exposure to trace amounts of PCBs. Such exposure is much less than that received by workers who made transformers or capacitors from the 1940s through the 1970s.



Chlorinated dibenzofurans may be responsible for the health effects attributed to PCBs.

Even workers with exposures two orders of magnitude greater than environmental exposures seem to show no convincing chronic health effects. In a number of capacitor plants, workers developed chloracne, a persistent skin disease that primarily affects hair follicles. Whether the chloracne resulted from PCB exposure or from exposure to chlorinated dibenzofurans, a known cause of chloracne and a possible contaminant of the PCBs, is unclear. There is reason to believe that chloracne and other health effects popularly associated with PCBs are really caused by chlorinated dibenzofurans.

In 1968 in Japan and in 1978-79 in Taiwan, two poisoning outbreaks took place in people who accidentally ate rice oil contaminated with a mixture of PCBs and polychlorinated dibenzofurans. The poisoning, called Yusho disease in Japan and Yu-cheng disease in Taiwan, led to chloracne and dark discolored skin among most of those exposed. Children were born with erupted teeth, and dentition of the permanent teeth was affected. Further, these people had many other acute health effects, such as abnormal liver and nerve function tests, abnormal menses, and persistent bronchitis. Babies were born with dark skin discoloration and low birth weight for term infants. In both episodes, later investigation established chlorinated dibenzofurans as the cause of poisoning.

One reason for this conclusion is that U.S. workers exposed to much higher PCB doses than patients with Yusho and Yu-cheng disease do not show the same health effects. Some workers complained of burning eyes, nose, and throat. Some studies reported abnormal liver function tests. One study, in a capacitor plant, noted abnormal lung function tests among the workers. However, these workers had also had other exposures that could have resulted in abnormal lung function tests.[4]

Attempts to conclusively demonstrate health effects in populations that eat fish from polluted waterways have generally failed. Occasional reports have noted behavioral changes and shorter pregnancies with higher fish consumption or higher intake of PCBs.[5,6] However, because these studies couldn't rule

out other causes, the significance of their findings is unclear.

Several occupational studies have presented no conclusive scientific evidence that PCBs have caused cancer in humans.[4] While one study found a positive association between PCB blood levels and high blood pressure,[6] the association appears spurious. The levels of PCBs in serum are primarily a function of the amount of fat present in serum. Serum PCB levels are, for instance, positively correlated with blood cholesterol levels.[6,7] The associations disappear when PCB levels are expressed as a function of fat in serum rather than as whole serum. In populations on Western diets, both serum fat levels and whole serum PCB levels increase with age. They are usually higher in males than in females, which corresponds with population survey findings that females usually have lower cholesterol levels than males in the same age group. Finally, the prevalence of elevated blood pressure also increases with age. In essence, all the associations go in tandem and appear to be spurious.

Thus, despite positive laboratory animal data and except for chloracne, exposure to PCBs has led to no convincing, clinically demonstrable, chronic health effects in humans.

*Members of the same chemical family; each member differs in the number or location of substituents.

References: 1. Kimbrough et al., Environ Health Persp. 24:1?+184, 19?8; *2. Kimbrough et al.*, Environ Health Persp. 59: 99-106, 1985; *3. Kimbrough et al.*, Ann. Rev Pharmacol. Toxicol. 27:8?-111, 198?; *4. Jacobson et al.*, Div Psychol. 20:523-532, 1984; *5. Fein et al.*, J. Pediatr. 102:315-320, 1984; *6. Kreiss et al.*, J. Am. Med. Assoc. 245:2505-2509, 1981; *7. Lawton et al.*, Environ. Health Persp. 60:165-184, 1985.

Commentary

Harnessing Natural Processes To Degrade PCBs.

by Michael A. Kamrin, Ph.D., Professor, Center for Environmental Toxicology, Michigan State University

As numerous analyses of air, water, sediments, wildlife, and other environmental samples have shown, PCBs are extremely persistent compounds found in all parts of the environment.

In ambient air and water, PCB levels are quite low. Even if one assumes a lifetime exposure to the highest measured levels all day every day, air and water offer a low risk of human exposure. Fish, however, appear to be a more significant source of PCBs. Why? First, PCBs bioaccumulate and biomagnify in the aquatic food chain. Further, as many people become more health conscious, they tend to eat more fish. For people who subsist almost entirely on fish they catch themselves, high environmental levels plus high consumption can lead to significant exposure.

Because fish are such an important source of PCBs, government agencies have taken steps to minimize this exposure. On the federal level, the Food and Drug Administration has set maximum tolerance levels for PCBs in fish sold in interstate commerce. To address intrastate consumption, some states publish fish advisories that recommend limited or no consumption of fish from bodies of water significantly contaminated with PCBs and other chemicals of concern. A number of states bordering Lake Michigan have collaborated on a common advisory for Lake Michigan fish.

PCB reservoirs

Limiting exposure by regulation or recommendation does not address the fundamental reservoirs of exposure—where PCBs are stored in the environment. Available data clearly indicate that the main sources of PCBs in fish are the sediments in contaminated rivers, lakes, streams, and estuaries. About one-third of all PCBs in the global environment are contained in fresh and saltwater sediments.

Most remaining environmental PCBs seem to be stored in open waters around the world, largely as a result of atmospheric transport and deposition. Despite worldwide dispersal, however, studies of oceanic life suggest that PCBs are not evenly distributed: the highest levels are in the northern hemisphere, especially at latitudes that encompass the industrial nations.

In addition to the large quantity of PCBs in the environment, an approximately equal amount is still in use, mainly in dielectric fluids in sealed electrical equipment. The most important step for limiting future exposure entails exercising great care in disposing of all PCB-containing materials still in service. In most cases, users of electrical equipment are taking care; continued vigilance

should spare the environment further insult from this source of PCBs.

Treating PCBs in the environment

PCBs already released, however, are more difficult to control. For example, PCBs are dispersed in consumer and commercial products in many sanitary landfills and private dumps. Because of careless disposal, PCBs from some sites have vaporized and contaminated the atmosphere. Locating and properly sealing disposal sites can help reduce the environmental burden.

Still, because sediments appear to be the most important reservoirs of human PCB exposure, this is clearly not enough. Because they are persistent, PCBs become less available mainly through burial, becoming covered by organic debris over time. The process is slow. While it takes place, disturbances of bottom sediments can resuspend PCB-laden particles to contaminate the food chain for years to come. Therefore, some environmental researchers advocate actively attempting to reduce environmental PCB levels, instead of waiting for nature to take its course.

One approach has been to dredge PCB-contaminated sediments for burial in secure landfills. This approach has not proven successful. Incineration, used to some degree to treat contaminated soils, is both time-consuming and costly, and would be even more expensive as a treatment for sediments.

Capitalizing on natural processes

More recently, a new effort has begun, based on the finding that PCBs in sediments are degraded naturally, probably through the action of microorganisms. The degradation seems to work by dechlorinating PCBs to form less chlorinated, and generally less toxic, congeners. Because natural dechlorination seems to be quite slow, researchers at Michigan State University have been looking into ways of improving on nature by enhancing degradation rates. A logical first step will be to determine if the degradation is caused by microorganisms and, if so, to isolate the organisms responsible.

If such organisms can be cultured and studied in the laboratory, it might be possible to increase the environmental degradation rate in a number of ways. One would be to enrich the soil or sediment with nutrients in such a way that the desired bacteria can increase greatly in abundance. In a related approach, investigators might seed an area with a large quantity of the organisms or, to maximize the effect, use a combination of enrichment and seeding. A third possibility is to genetically engineer non-PCB degrading organisms to contain the genes responsible for the degradation capacity. Introduced into the environment under the right conditions, these organisms could multiply on their own and dechlorinate PCBs rapidly.

If successful, these methods would provide a means of *in situ* destruction that could avoid the negative aspects of other disposal methods, such as air pollution from incineration or possible spillage during transport to a secure site. Regardless of the efficiency of new techniques, the volume of PCBs already in the environment is so large and so dispersed that they will be with us for a long time to come. The hope is that their levels can be significantly reduced in critical locations to minimize the chance of human or animal PCB exposure. Though we can't put the genie back in the bottle, it's important that we tame it as much as possible.

Suggested Reading: Tanabe, S., "PCB Problems in the Future: Foresight from Current Knowledge," Environmental Pollution 50, 5-28, 1988; D'Itri, F. M. and M.A. Kamrin, eds., PCBs: Human and Environmental Hazards, Ann Arbor Science, 1983.

Readers Forum

Minamata Disease

As the Update report from New Jersey points out, a lack of integrated response from government agencies, limited implementation of regulations, and poor communication can create environmental problems and hamstring their management. The history below reviews a case in which such conditions had disastrous effects.

In April 1956, the Chisso Corporation's factory hospital in Minamata, Japan, began to admit a number of patients with delirium, disturbed speech, and abnormal gait. In May, the hospital's director reported the outbreak of unknown disease of the central nervous system (CNS) to the Minamata Dept. of Public Health. By December 1974, 798 patients with "Minamata Disease" had been officially recognized; 107 had died; 2800 others had applied for recognition. Forty cases resulted from exposure *in utero*.

Symptoms included sensory loss; ataxia; impaired speech, hearing, and gait; difficulty in chewing and swallowing; involuntary movements; and bilateral

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The *Digest* draws on the expertise of a network of representatives in 22 schools of public health, 50 state health departments, and over 75 research institutions, government agencies, state public health associations, and medical societies. Start-up funds were provided by a grant from the Bush Foundation.

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HUMAN HEALTH EFFECTS

OF

ELECTRICAL-GRADE PCB's

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Abbreviations which may be unfamiliar to some readers include:

ppm	parts per million
ppb	parts per billion
kg	kilogram; 1000 grams
gm	gram (s)
mg	milligram(s); one thousandth of a gram
$\mu g/m^3$	micrograms (millionths of a gram) per cubic meter
µg/L	micrograms per liter (approx. = ppb)
LD_{50}	an acute toxicity measurement meaning dose lethal for 50% of the test animals
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GGTP	Liver serum enzyme gamma glutamyl transpeptidase
HEW	Health, Education and Welfare Department (now called Health and Human Resources Department)
NIOSH	National Institute for Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
p,p'-DDE	Metabolite of DDT present as background in blood analyses
SGOT	Liver serum enzyme glutamic oxaloacetic transaminase
TLV	Threshold Limit Value: an exposure concentration representing conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect.

Although the production of polychlorinated biphenyls (PCB's) in the U.S. has been banned, definition of the human health risks they may pose continues to be an important issue. The PCB's were widely used for nearly 50 years, chiefly as dielectric fluids and plasticizers, and large amounts are still present in electrical equipment that will require servicing and disposal. PCB's are also present in numerous environments that may, or may not, merit containment or restorative actions. Small, but measureable levels are found in some edible fish. Thus, the potential for human exposure to PCB's remains.

At present, Company managers, employees, physicians and public officials concerned with appropriate handling of these exposure situations face a contradictory array of information on the possible health hazards. On the one hand, the U. S. press and environmental literature (e.g., ref. 1) increasingly portray PCB's as very toxic materials, and situations resulting in human exposure at any level as hazardous and alarming. The Toxic Substances Control Act of 1976 (TSCA) and attendant regulations generally ban PCB manufacture, processing and distribution; severely limit use; and impose strict requirements for PCB labeling, disposal and storage for disposal.

On the other hand, many European countries have made a quite different risk/benefit assessment of PCB's since they continue to permit PCB manufacture and use in closed electrical equipment. More importantly, 40 years of U.S. occupational exposure in capacitor manufacturing has proven relatively uneventful, as judged by documented adverse health effects.

Many medical studies or observations of human populations that were heavily exposed to PCB's have been reported (2,3,4,5,6,7,8,9,10,11,12,13, 14,15,16,17,18,19,20,33,47,49,50,51,52,55,56,59,60,61,63). Some of these investigations are very recent and have only become available since the public image of PCB's was formed. Not all are yet reported in the published literature. The authors have undertaken this paper to provide perspective for General Electric managers and physicians, and to help identify situations of human exposure to PCB's that might present cause for concern. It draws on extensive GE experience in plants manufacturing PCB-filled capacitors, as well as on review of the scientific literature. The paper reflects today's knowledge and may be extended if significant new information becomes available. The concluding section describes on-going research that may provide additional information relevant to some present uncertainties.

This paper presents many quantitative observations because these are critically important to any health effects perspective. The fact that PCB's are persistent and readily detectable at low concentrations does not necessarily mean that they are toxicologically significant.

**As used throughout this paper "electrical-grade PCB's" describes various PCB's used in GE capacitors and transformers.*

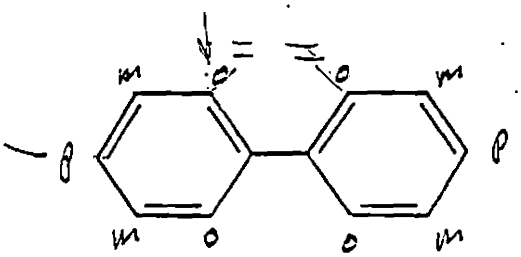
Section I

Introduction

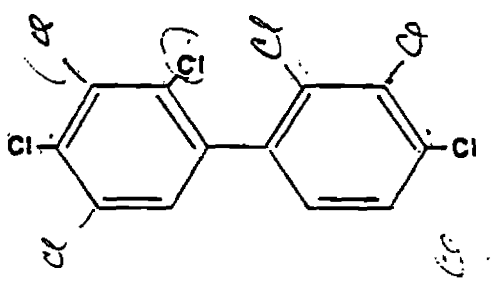
The PCB bioeffects literature is voluminous, comprising several hundred original articles. The present paper will not attempt to survey all aspects of this information, but will focus on those portions the authors judge most relevant to human health effects evaluation. In addition to literature citations the bibliography lists health-related conference reports (21,22,23,24,25) and several review books and documents (26,27,28,29,30).

PCB Composition and Terminology

In chemical terminology "phenyl" denotes a ring structure of six carbon atoms attached to something else; "biphenyl" results when two such rings are attached to each other; and a "polychlorinated biphenyl" (PCB) is any molecule having multiple chlorine atoms attached to the carbon atoms of a biphenyl nucleus. Biphenyl and a representative trichlorobiphenyl (PCB) are illustrated below:



Biphenyl



2,4,4'-Trichlorobiphenyl (a PCB)

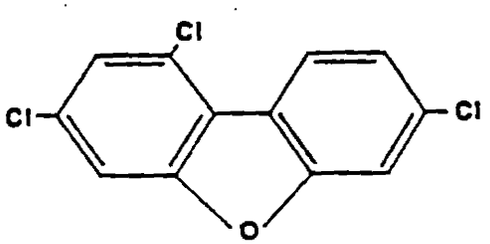
There are 209 theoretically possible chlorinated biphenyl molecules, differing in the numbers (homologs) and positions (isomers) of the attached chlorines; of these 209 species, about half have been identified as being present among the complex mixtures that constitute commercial PCB products. These products range from light oily fluids (di-, tri-, and tetra-chlorobiphenyls) to heavy, honey-like oils (penta-chlorobiphenyls) to greases and waxes (more highly chlorinated).

The manufacturers of PCB's sold them under trade names; e.g., "Aroclor" (Monsanto, USA), "Phenoclor" and "Pyralene" (Prodelec S.A., France), "Clophen" (Farbenfabriken Bayer AG, Germany), or "Kanechlor" (Kanegafuchi Chemical Industrial Co. Ltd., Japan). They also assigned product numbers that usually reflected either the average degree of chlorination or, what is equivalent, the weight-percent chlorine in the mixture. Thus, the American Aroclor 1242, its French equivalent, Phenoclor DP3, and its Japanese equivalent, Kanechlor 300, all contained 42% chlorine, or 3 chlorine atoms per biphenyl on the average. Likewise, Aroclor 1254 and its German equivalent, Clophen A50, contained 54% chlorine, or 5 chlorine atoms per biphenyl on the average. Aroclor 1016 designated a Monsanto PCB product similar to Aroclor 1242 with enhanced biodegradability, which was accomplished by removal of higher chlorinated homologs.

Electrical equipment manufacturers further purified these commercial PCB products to insure electrical performance; blended them with stabilizers and diluents; and then put the resultant PCB mixtures into capacitors and transformers under their own trade names and product numbers. GE's trade name for its PCB mixtures was "Pyranol." "Askarel" is a generic, industry-wide term for a PCB or other fire-resistant dielectric fluid.

In short, the materials now collectively referred to as "PCB's" are different complex mixtures of chlorinated biphenyls used under a variety of product names. These mixtures always contained several dozen individual PCB isomers and homologs clustered around some average degree of chlorination, frequently some trichlorobenzenes as diluents; often about 0.5% of an aliphatic epoxide as a stabilizer; and parts-per-million levels of trace impurities such as the polychlorinated derivatives of methylbiphenyls, terphenyls, naphthalene or dibenzofuran.

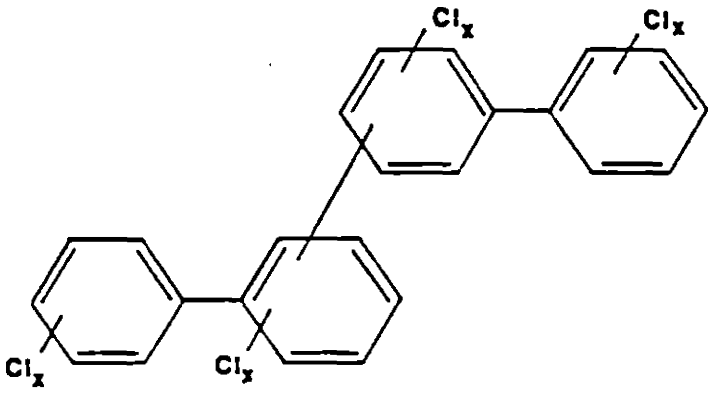
Returning to chemical terminology, "furan" denotes a ring structure of four carbon atoms and one oxygen atom; and "dibenzofuran" a tricyclic arrangement of two benzene rings and one furan ring fused together. This structure can result if an oxygen atom is added to a biphenyl system. If multiple chlorine atoms are attached to this nucleus, then a "polychlorinated dibenzofuran", or PCDF, results as illustrated below. There are 135 theoretically possible chlorinated dibenzofurans.



1,3,7-Trichlorodibenzofuran (a PCDF)

Trace levels of PCDF's have been detected in laboratory samples of U. S. PCB's, including specimens of both individually synthesized isomers and commercial mixtures (32,37). There are two plausible explanations for the presence of PCDF's in commercial PCB's: First, contamination may have occurred during manufacture, possibly as a result of oxygen in the benzene used to make the original biphenyl. Such contamination may have existed in French and Japanese PCB's, but apparently was not significantly present in American-made PCB's after one episode in 1933. Second, PCDF's may have been formed during usage as a result of high temperature oxidation. Oxidation experiments (31) report maximum conversion of Aroclor 1254 to total PCDF's as 2-3% at 550-600°C. Conditions suitable for significant conversion of PCB's to PCDF's did not exist in the normal manufacture of, and are not expected in the normal use of, capacitors and transformers, but may occur in high-temperature heat exchangers.

A related group of molecular species mentioned in this paper are the polychlorinated quaterphenyls (PCQ's), which contain four phenyl units and a variable number of chlorine atoms as illustrated below:



Polychlorinated quaterphenyl (PCQ)

History of PCB Use

The Swann Chemical Co. began commercial U.S. production of PCB's in 1929. In 1935 Monsanto Industrial Chemicals Co. (Monsanto) purchased Swann and continued the manufacture of PCB's, initially at Anniston, Ala. and later at Sauget, Ill.

PCB's are excellent non-flammable, high-boiling, thermally and chemically stable dielectrics and solvents, and these properties led to a wide range of industrial applications. In addition to serving as dielectric fluids in capacitors and transformers, PCB's were used as plasticizers, hydraulic and heat exchange fluids, and were incorporated into such products as dust-settling agents, die-casting lubricants, inks, dyes, paints, pesticides and adhesives. PCB's were widely used in carbonless reproduction paper and entered paperboard production.

PCB's from such sources have entered into the environment. Slow biodegradability and bioaccumulation account for the presence of PCB's in sediments under rivers and lakes and in fish. Trace quantities have been found in some other food as well. As a result, PCB's are found in trace quantities in the blood and fatty tissue of the human populations of all industrial nations.

Concern over such accumulations in the environment led Monsanto in 1970 to begin voluntarily restricting PCB sales to manufacturers of sealed electrical equipment (33). In 1976 Congress enacted TSCA, which mandated a phaseout of PCB production and use. Although similar PCB phaseouts were instituted in Japan, Canada and Sweden, many other industrial nations (e.g., U.K., Germany, France, Spain and others) continue to permit PCB production and the manufacture of PCB-filled capacitors and transformers.

Estimates (34) for the cumulative total of U.S. industrial uses of PCB's from 1930 to 1975 and their service status in 1976 are noted in Table 1 below:

Table I

	Millions of Pounds	
Use	Industrial PCB Purchases	PCB's Currently in Service
Capacitors	630	450
Transformers	335	300
Plasticizers	115	↑
Hydraulics and Lubricants	80	|
Carbonless copy paper	45	8
Misc. industrial	28	|
Heat transfer	20	↓
Total	1253	758

Estimates (34) of the status of these PCB's are shown in Table II below:

Table II

Disposition	Millions of Pounds
Environmentally biodegraded	30
Incinerated	25
Landfills and dumps	290
In soil, water, air and sediment	150
Currently in electrical service	750
In use other than electrical service	8
Total	1253

A. Observations on Test Animals

1. General Bioeffects PCB's resemble other fat-soluble chlorinated organic chemicals in biological uptake and internal transport. An animal can readily absorb PCB's through the lungs upon inhalation or through the intestines following ingestion, or less readily through the skin after physical contact. Fish can absorb PCB's through the food chain or through their gills, and the bioconcentration factors* can range between 10^3 and 10^6. Once inside the body PCB's gradually distribute themselves equally among all fatty deposits present. Elimination processes are generally slow, especially for the more highly chlorinated homologs.

When increasing doses of PCB's are administered to animals the first observable effect is the induction, primarily in the liver, of the cellular enzymes variously known as "drug metabolizing" or "detoxification" enzymes, or as "mixed function" (i.e., chemically non-specific) oxidases. These enzymes catalyze chemical processes by which the animal's body seeks to convert lipid-soluble foreign chemicals into water-soluble substances excretable in the urine. Such effects are also produced by many other substances, and are generally regarded as physiological rather than pathological processes.

At high enough doses in animals, PCB's can induce many types of toxic effects and eventually death. The reported toxic effects with chronic exposure include chick edema disease and teratogenesis in chickens; liver hypertrophy, fibrosis, neoplasia and cancer in rodents; gastric and dermatological lesions in monkeys; and reproductive dysfunction in several species. An extensive literature on this subject is referenced in the bibliography (21-30).

There can be differences in toxicity between different PCB products, with the higher homologs generally being reported more toxic in chronic tests and the lower homologs more toxic in acute tests. There can also be large toxicity differences observed between different specimens of the same type of PCB, apparently caused by impurity-level variations.

2. Impurity Effects In 1970 a Dutch scientist, J.G. Vos, observed striking differences in chick embryotoxicity among three commercial PCB's that all contained 60% chlorine: Aroclor 1260 (which had virtually no effect), Clophen A60, and Phenoclor DP6. He then demonstrated that the variable toxic agent in the system was an impurity, polychlorinated dibenzofuran (PCDF) (35). He also showed that this impurity was responsible for chloracne in PCB dermal tests with rabbits (36).

It is not possible to determine if the toxic response variabilities observed in other PCB animal tests should be ascribed to variations in PCDF levels because, unfortunately, few of the investigators reported impurity levels in the PCB specimens they tested. Chemical analyses have sub-

*A bioconcentration factor is defined as the ratio of the PCB concentration in a fish to that in its ambient water

sequently reported that European and Japanese PCB's contained 5-20 ppm PCDF as manufactured, while the U.S.-made Aroclors had 0-2 ppm (37).

3. Structure-Activity Relationships Many recent animal studies have aimed at relating the molecular structures of individual PCB, PCDF or similar molecules to their biological activities. These studies have shown that chloracnegenic activity is specifically associated with molecules shaped like flat rectangles with chlorines at the corners (32). All such chloracnegenic species are also capable of inducing one specific type of mixed function oxidase, designated cytochrome P448 because of its spectral absorption band position.

Most lower homolog PCB molecules do not induce P448; however, some higher chlorinated PCB homologs, which constitute a few percent of the higher Aroclors and which are virtually absent from the lower Aroclors, do exhibit moderate P448-inducing activity. By comparison, 2,3,7,8 -tetrachlorodibenzofuran is 700 times as potent a P448 inducer in rats as the active PCB isomers and is many orders of magnitude more biologically potent than most other PCB and PCDF molecules (26 chap. 6).

4. Toxicity and Carcinogenicity Test Results Toxicity testing of PCB's in experimental animals has produced a large body of experimental observations. Repeated short-term feeding tests have shown the acute toxicities of PCB's in animals to be low, with LD_{50} values reported from 1,300 to 11,300 mg per kg of body weight (29).

Concerns over chronic human health effects of chlorinated aromatic hydrocarbons (including PCB's) led to a series of 3-4 month inhalation tests in animals at the Harvard School of Public Health in the 1930's (38) and confirmatory tests at the University of Cincinnati's Kettering Laboratory in the 1950's (39). From the observations in both test series the investigators recommended threshold limit values (TLV's) of 1000 $\mu g/m^3$ for PCB's with 42% chlorine or less, and 500 $\mu g/m^3$ for the more highly chlorinated PCB mixtures. These TLV's, used by industry during the remaining period of PCB use, were accepted as standards by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1956, and by OSHA in 1971, and were adopted by many other countries as well.

When PCB's are chronically administered to rats in increasing doses, there is apparently a dose-related progression from "no-effect", to mild, reversible effects (40) to serious irreversible liver disease. The observed progression of effects on rodent livers includes cellular enzyme induction, microsomal proliferation, cellular hypertrophy, focal necrosis, fibrosis and eventually the development of increasingly abnormal types of tissue (41,42, 43). In some of these tests in rodents, PCB's have been judged to show carcinogenic activity, while in other tests the same materials (Aroclor 1254 and 1260) were judged not to have shown carcinogenic activity (33, 42,43, 44).

Reports of positive carcinogenic findings in long-term tests of substances in rodents at high dosage levels, while prompting caution with respect to human exposure, are not an uncommon observation. General Electric has noted that in HEW's "Survey of Compounds Which Have Been Tested for Carcinogenic Activity", PHS Document 149, Vols, 4,5,6, & 7, 70% to 80% of all substances tested from 1960 to 1973 were reported to produce excess tumors in animals (45,46).

B. Human Health Effects Observations

1. Early Occupational Chloracne Reports During the first 35 years that PCB's were in industrial use, three American medical reports described unambiguous episodes of PCB-linked occupational illness.* Two involved PCB vapors from high-temperature equipment, and the other was ascribed to an unidentified impurity.

The first episode occurred in 1933 at the Swann Chemical Co. when 23 of 24 men working on the manufacture of PCB's almost simultaneously developed skin eruptions diagnosed as "chloracne." The eruptions were similar to adolescent acne, i.e., a progression of blackheads and pustules that persisted several months before disappearing. Some of the men also complained of lassitude but showed no clinical signs of ill health other than the skin condition. In their report on this PCB episode, the investigators concluded that the toxic agent was probably an unidentified impurity that appeared in the PCB when a new source of crude benzene was used for making the biphenyl (47). When purchase from this benzene source was discontinued and the process equipment better enclosed, the problem disappeared.

Chloracne was known by this time to be induced by chlorinated coal tar products and by chlorinated naphthalenes (Halowaxes). Later, occupational chloracne was frequently observed among electrical workers who handled "cable wax" containing the latter materials. Chloracne was found to clear up some time after the contact was removed and improved hygiene instituted. Concerns about long-term effects of chloracne have been addressed by a recent study, in which a group of 121 male chemical workers who had experienced a chloracne attack in 1949 (unrelated to PCB's) showed no excess in total mortality nor in cancer mortality after 29 years (48). A background incidence of chloracne in children in Northern Italy has been reported as 0.1-0.5% (26, p.331).

The second episode involving PCB's occurred in 1950 and 1951, when 7 of 14 people exposed to vapors (reported at 100 $\mu g/m^3$) from a leaky PCB-containing heat exchanger developed chloracne (49). A third episode was noted in the early 1960's when 13 of 16 people exposed to vapors from an oven in which PCB-plasticized enamels were being baked were similarly affected (50).

Some other early papers confusingly associated PCB's with the health effects of certain other chlorinated hydrocarbons.

2. Yusho Episode Despite the long and relatively uneventful PCB occupational exposure experience the Japanese "Yusho" (oil-disease) incident in 1968 created a wave of concern. In that episode some 1300 people in southwestern Japan developed a very severe and persistent form of chloracne after eating rice oil found to have been contaminated by fluid leakage from a heat exchanger originally filled with Kanechlor 400, a Japanese PCB (51).*

In addition to the acne-like eruptions and feelings of lassitude previously observed in chloracne outbreaks, the Yusho victims commonly exhibited swelling of the upper eyelids, increased eye discharge, hyperpigmentation of the nails and skin, sweating of the palms and a variety of other individual effects. Signs of the disease were also transmitted in some cases to newborn children. The brown dermal pigmentation of these children is reported to have diminished with time. (26 chap. 9B1). In the same period a chick edema epidemic that killed 400,000 chickens was traced to consumption of feed containing the same rice oil. The first contaminant to be identified in the rice oil was Kanechlor, and a widespread demand for controls or elimination of all PCB's resulted.

After the Vos identification of PCDF impurities as the active toxic agent in two PCB animal test sytems, Japanese scientists reanalyzed some of the rice oil specimens that had caused Yusho illness (52). From 1975 to 1978 it became known that these rice oil samples contained about 1000 ppm PCB's, 5 ppm PCDF's and 1000 ppm of another chlorinated material, later identified as polychlorinated quaterphenyl (52,53,54). The PCDF's and PCQ's presumably were formed from PCB's by thermal oxidation and condensation in the heat exchanger at high temperature. The apparent PCDF content of the leaking heat exchanger fluid, calculated from the above analysis of rice oil contaminants, is 2500 ppm (0.25%), a very high level compared to PCDF levels in U.S. electrical-grade PCB's as manufactured (0-2 ppm).

As the Yusho victims were estimated to have ingested an average of 2.0 gm of the heat exchanger fluid (51), this amount would have included about 1.0 gm each of PCB and PCQ, along with approximately 5 mg of PCDF. As will be noted later, 1.0 gm of PCB is less than the average body burden of heavily exposed capacitor workers; however, the Yusho victims apparently eliminated their PCB burdens more rapidly than capacitor workers, exhibiting nearly normal background levels of PCB's after 5 years. Nonetheless, many Yusho patients remained sick, and such autopsy liver samples as became available showed concentration of penta- and hexa-chlorinated PCDF's in that organ (52).

**A second episode, involving essentially identical circumstances and consequences, has just been reported from Taiwan (59).*

These later Japanese investigations linked the disease to the PCDF content of the rice oil. This conclusion is consistent with PCDF activity in animal tests and with the observation that body burdens of electrical-grade PCB's (from inhalation and skin contact) larger than the PCB doses ingested by Yusho victims have not induced Yusho illness in capacitor workers.

The Japanese Yusho investigators also reported that the minimum dose for induction of the disease was about 0.5 gm of the thermally decomposed heat exchange fluid (the PCB-PCQ-PCDF mixture) (51). Using a range of reported PCDF analyses (52), the PCDF toxicity threshold dose might therefore be estimated at 1.0 - 1.5 mg.* A similar threshold dose (1.26 mg) has been estimated from data on the amount of PCDF consumed by patients before the onset of the symptoms in the recent episode in Taiwan (60).

3. Effects of Eating Fish Containing PCB's The Michigan Department of Public Health, under the sponsorship of FDA, conducted a study of 182 adults, 105 of whom consumed over 26 pounds of Great Lakes fish per year. A significant correlation between blood PCB levels and quantity of fish eaten was observed. The mean blood PCB value for the exposed group was 73 ppb, while that of the comparison group was 20 ppb. Individual blood PCB levels ranged from 7 ppb for a person who ate no fish to 366 ppb for one who ate 132 pounds per year (11,12).

Evaluation of health histories and current medical problems of the study subjects failed to identify a significant difference between the exposed and comparison groups. Symptoms characteristic of reported PCB toxicity (Yusho symptoms) were not found nor did those with the highest PCB levels have a consistent pattern of complaints or conditions. Although the data demonstrate an association between fish consumption and PCB levels in humans, no toxic manifestations from this exposure have been identified to date (12). The question of PCB accumulation over time and the effects of long-term exposure are being evaluated in a continuation of this study.

A recent study (61) of 458 persons who had significant exposure to DDT from eating fish also reported PCB blood levels (arithmetic mean, 22 µg/L; range 3.2 to 158 µg/L). The authors report that the following significant correlates of log diastolic blood pressure might account for 24.1% of its variation in this cohort: body mass index, 6.8%; sex, 8.3%; log PCB level, 6.3%; age, 1.5%; Hollingshead index, 1.1%.

4. Clinical Studies of Capacitor Workers The most extensive long-term exposure of humans to PCB's has probably occurred in capacitor plants around the world. (There were 17 capacitor plants using PCB's in

A recent reanalysis of YUSHO patient data puts this figure at 0.6 mg. (26 p. 291)

the U.S.) Many employees in these plants had daily PCB skin contact for several years and inhaled PCB's at levels in the 100 to 1000 $\mu g/m^3$ range. General Electric's major capacitor fluid usage was originally Aroclor 1254, then changed to Aroclor 1242 around 1954, and subsequently to Aroclor 1016 (and some 1221) in 1971. This usage pattern was probably typical of the industry.

PCB blood tests of 174 heavily exposed GE capacitor workers have indicated a geometric mean* around 300 ppb and an arithmetic mean of about 500 ppb. Ten percent of the individuals' analyses were above 1000 ppb. A blood PCB value of 300 ppb roughly corresponds to a 100 ppm level in fatty tissue of the same individual, or a body content of about 1.5 gm (16). By comparison, mean serum PCB background levels for various groups of industrially unexposed persons in the U.S. range from 2-24 ppb (26 p.269).

In capacitor plants the most frequent PCB-related health effect observed was transient skin rashes affecting a small percentage of exposed employees. For example, analysis of GE medical records of the Ft. Edward and Hudson Falls, N.Y. plants for the 1960-1975 period showed a cumulative total of 49 contact and allergic dermatitis cases attributed to PCB's among an exposed employee group totalling about 1300 individuals (5). This condition responded to simple topical treatment and employee reassignment to other work areas. The medical records of this worker population have shown no obvious incidence of systemic disease attributable to PCB's. Additional studies (described below) are continuing.

Observations of high PCB blood levels, some dermal conditions and isolated cases of chloracne have been reported in the industrial hygiene literature of Japan, Finland, Australia and Italy (2,3,4,6,7,8). The reported biochemical examinations (2,3,4,6,7) identified scattered individual abnormalities in serum enzymes; however, on a group basis the various liver function tests were considered normal. The Italian chloracne cases of ref. 7 were observed in men who had worked where the level of Aroclor 1254 was measured at 5200-6800 $\mu g/m^3$ (10-14 times the U.S. TLV). Ref. 4 states that the Finnish capacitor workers are in good health and that, in spite of approximately 50 times larger PCB concentration in their blood compared with a control group, the researchers were unable to detect any biological effect caused by PCB in them.

In a 1977 U.S. study 32 capacitor workers were examined in a program sponsored by the South Carolina State Department of Health and Environmental Control (DHEC). Newspaper reports (January 1978) quote Dr. D.H. Robinson of the DHEC as saying that the study "clearly shows that at present there is no evidence of physical harm resulting from working with PCB's." Dr. Ira Rosenblum of Albany Medical College, who directed the study, is also quoted as stating, "It is exceedingly difficult

*The geometric mean of n numbers equals the nth root of their product. For a log normally distributed population the geometric mean equals the median.

to establish a cause-effect relationship between exposure to PCB's in the workers' environment and any sign or symptom of acute disease of occupational origin (9)."

A study of occupationally exposed Bloomington, Ind. capacitor workers and other residents, reported in 1978, did not note liver injury, but found that levels of GGTP liver enzyme and plasma triglycerides were positively correlated with those of serum PCB's (10). No correlations were observed between serum PCB levels and five other liver function indicators. A letter to the study participants from the U.S. Center for Disease Control noted that human cancer risk would remain unknown until the extensive mortality study (reported below, ref. 15) then being conducted by NIOSH had been completed.

A broader clinical study of 224 Bloomington, Ind. capacitor workers was later conducted by NIOSH. The investigators reported in a preliminary draft (1981) that the plant employees' serum L-PCB levels* were 8 to 50 times, and their serum H-PCB levels* 2 to 4 times, the community background level (17). A parallel study was also conducted of 92 employees in two electric utilities, 39 of whom were active in the maintenance, repair and overhaul of transformers (18). A draft report covering both studies (63) stated that no clinical abnormalities directly attributable to PCB exposure were observed on physical examination. Serum SGOT, GGTP, triglycerides and HDL-cholesterol were within normal ranges. The first three of these parameters were correlated positively, and the last, negatively, with serum PCB levels.

One report at variance with this pattern of clinical studies describes a recently published study of 80 Italian capacitor workers who were chronically exposed to French and Italian PCB's containing 42% chlorine. PCB concentrations in air were reported from 48-275 $\mu g/m^3$, and skin absorption was noted. Fifteen of the 80 exhibited skin abnormalities, including 4 diagnosed as chloracne. Sixteen other workers were judged to show more or less pronounced hepatic involvement, as deduced from symptoms, clinical examination of the liver, and serum enzymes (19,20).

In 1976 Dr. Irving Selikoff of Mt. Sinai School of Medicine began a study of the health status of capacitor workers in the GE plants at Hudson Falls/Ft. Edward, N.Y. Three hundred twenty-six volunteers, some of whom had a long history of occupational exposure to PCB's, were given extensive medical examinations. In one paper the investigators reported average PCB blood levels of 124 ppb (lower homologs) plus 48 ppb (higher homologs) and noted a correlation between individual values and the estimated job exposure. A number of dermatological findings were reported, some of which showed an association with blood PCB levels of the higher

**L-PCB (lower homologs) and H-PCB (higher homologs) are defined as species having respectively shorter and longer gas chromatographic retention times than p,p'-DDE.*

homologs. The authors noted a paucity of other abnormal findings on physical examination, including a very low prevalence of abnormal liver findings (13). In another 1979 paper the Mt. Sinai group reported that 14% of the workers examined had abnormal vital (lung) capacity, compared with 5.6% cited for Morris' non-smoking normal population (14, 62). We believe the significance of this observation is uncertain.

Medical surveillance by General Electric of a group of 174 heavily exposed capacitor workers has consisted of multiple examinations over the last four years. The GE service of this group averages over 15 years, and ranges from 1 to 35 years. About 20% of this study population is overweight, shows elevated serum triglycerides and periodic, mild elevations of fasting blood sugar. However, the medical examinations have not revealed serious health problems related to PCB exposure. The pulmonary function tests of the non-smokers in this heavily exposed population were in the normal range.

As previously noted, the serum PCB levels in this group are high (1979 arithmetic mean of 500 ppb with 10% of the individual analyses above 1000 ppb) and persistent. The only clinical parameter thus far found to be statistically correlated with the serum PCB level is that of serum triglycerides. The interpretation of this correlation is confounded by the fact that PCB's distribute equally among all lipid pools in the body, including those in the blood; and hence for any given PCB body burden the serum PCB level must vary directly as the level of serum lipids.

A rough correlation which is emerging from this study of GE capacitor workers is that people who are exposed to airborne PCB's for long periods may show an increase of about 0.5 ppb in their blood for each 1 $\mu g/m^3$ present. Thus long-term environmental exposure to air containing 2 $\mu g/m^3$ PCB might be expected to add about 1 ppb to an average person's 2-24 ppb PCB background level, a small amount compared with the normal background, and insignificant compared to levels reported in heavily exposed capacitor workers (30-3000 ppb ref. 17).

5. NIOSH Mortality Study. Three preliminary reports have suggested a possible epidemiological association between PCB exposure and human cancer (33,55,56). All of these have been regarded as inconclusive because they involved small groups of people, few deaths, uncertain levels of exposure to PCB's and to other chemicals, short latency intervals, and lack of consistency in cancer site. The International Agency for Research on Cancer evaluated the evidence available through 1979 for PCB's causing cancer in humans as "inadequate", meaning "insufficient to allow any conclusion regarding carcinogenicity for humans" (30). The FDA's assessment in 1979, based on review of both animal tests and the human reports, was that the question of carcinogenicity of PCB's was unresolved, though a matter worthy of further inquiry (57). Shortly thereafter, more definitive evidence became available from a long-term NIOSH study of two PCB-exposed capacitor worker populations.

A report of this NIOSH mortality study (15), by far the most comprehensive ever conducted concerning human PCB exposure, provides the best current data on mortality experience. This retrospective cohort, standardized mortality study includes 2567 PCB-exposed hourly capacitor workers in two plants, one of which was the GE Hudson Falls/Ft. Edward, N.Y. complex. The cohort was defined as all workers who accumulated at least three months employment in areas of the plant where there was potential for exposure to PCB's. Exposure in one plant began as early as 1938, in the other by 1946. A total of 39,018 person-years had been accumulated by the January 1, 1976 study cutoff. Personal air samples in the plants in April, 1977 ranged from 24 to 1260 $\mu g/m^3$ and area air samples from 3 to 810 $\mu g/m^3$ PCB's.

The NIOSH study reported that the incidence of all cancer mortality for these plant populations was slightly lower than that of the general U.S. population, or 39 deaths due to malignant neoplasms vs. 43.79 expected based on national norms adjusted for age and sex. For other causes of death the findings were as follows: from cardiovascular disease, 60 vs. 62.93 expected; from nervous system disease, 11 vs. 12.55 expected; from accidents, 13 vs. 18.29 expected; and from all other causes, 40 vs. 44.79 expected. Deaths from all causes were 163 vs. 182.35 expected.

No statistically significant excesses of specific cancer types were observed, though the authors called attention to four rectal and three liver cancer cases (5 of 7 in one plant). We believe this observation should be followed up by extension of the study time span, because these reported rectal and liver cancer cases are too few to be statistically meaningful. Liver cirrhosis deaths were higher than normal in one plant (with the possibility of some alcohol association noted) and lower in the other, with the total cohort experience about equal to national norms. None of the causes of death analyzed demonstrated a clear association with latency. There was no clear relationship between increasing lengths of employment in PCB-exposed jobs and the risk of mortality due to cancer or cirrhosis of the liver.

While the mortality experience reported in this paper is reassuring, it should be recognized that even this large study does not yet encompass enough person-years of experience to exclude the possibility that there might have been increased risk of some uncommon type of disease. Further, the plant populations described were not segregated between those in lightly vs. those in more heavily exposed jobs, which might have provided more data concerning dose-related differences.

C. Health Effects Summary

To summarize, there is now available a scientific literature of several hundred papers describing many facets of the biological behavior of PCB's in animals: routes and rates of uptake and elimination; bioaccumulation and persistence; enzyme induction; other pharmacological effects; and the effects of molecular structures of individual PCB molecules or impurites on biological activity. This literature includes early toxicological studies that led to recommendations to limit continuous occupational PCB exposure to 500 or 1000 $\mu g/m^3$ (depending on the degree of chlorination).

Nearly 50 years of experience has shown that electrical-grade PCB's, at industrial occupational exposure levels, are not acutely toxic to humans. A continuing concern about these materials has been potential chronic effects, since exposure to PCB's leads to accumulation in the body and retention for long time periods. The largest available source of data on such effects is presented by capacitor worker populations.

Thousands of such individuals received light to heavy exposures to PCB's of Aroclor types 1254, 1242, and 1016 over many years, and elevated levels of PCB's in their blood and fatty tissues continue to be observed. A number of clinical studies of such exposed worker groups have now been completed (2,3,4,5,6,7,8,9,10,13,14,16,17,19,20,63). Dermal reactions were noted in some cases. These included some rare observations of chloracne, especially in plants outside the U.S. Some studies report correlation of serum enzymes and triglycerides with serum PCB levels. In sum, the preponderance of these studies neither identify significant clinical disease associated with electrical-grade PCB exposure, nor provide persuasive evidence of health impairment. In addition, the NIOSH study of the long-term mortality experience of a large group of hourly capacitor workers at two plants showed no excess in total mortality, nor in mortality due to cancer, to cardiovascular disease or to nervous system disease.

A human hazard that was not recognized early was the possibility that PCB's used in high temperature environments, such as heat exchangers or baking operations at 270°C and higher, could be partially oxidized to PCDF's with a consequent increase in toxicity. This factor makes the YUSHO episode not directly relevant to the usual U.S. occupational or environmental exposure. Even in such special cases the health risk appears to be finite. The Japanese and Taiwanese Yusho investigations both provide evidence that the PCDF threshold dose for inducing Yusho illness is 0.6-1.5 mg. This may provide a benchmark for evaluating PCDF risk and for considering whether protective measures are needed when a PCDF level is identified in an environment (as, for example, in air with PCB's which have been overheated, or as trace quantities in the edible portion of fish). The available analyses indicate that U.S. electrical-grade PCB's contained 0-2 ppm PCDF's as manufactured. Such levels may be consider-

ed toxicologically insignificant since intake of about a kilogram of such PCB would be needed to acquire a threshold dose of PCDF. However, additional measurements are needed to check the PCDF levels in used PCB's.

In view of the lack of evidence for health damage in people with heavy PCB exposure in the past (daily skin contact and inhalation of air containing 100-1000 $\mu g/m^3$), there does not presently seem to be a substantial basis for concern about the effects of exposure to environments containing electrical-grade PCB's at the greatly reduced levels typically encountered today. Accordingly, while a confirmed blood or fat tissue PCB analysis* significantly higher than the local average may indicate exposure, there is little reason to believe that significant adverse health effects will occur. In the light of our present knowledge there is no further examination procedure or therapy which is likely to be meaningful.

While the lack of evidence for serious effects of electrical-grade PCB exposure on capacitor workers is encouraging, the studies available today do not completely rule out the possibility of subtle or infrequent effects in some individuals who were heavily exposed in the past, and more observation time is needed to reduce uncertainty about the very long-term experience of these people. Concerns about the reproductive experience of heavily exposed individuals also need to be addressed. The concluding section of this paper describes some on-going research programs that may resolve some of these uncertainties.

Any unconfirmed single PCB analysis should be regarded cautiously: a recent round-robin study by the N.Y. State Department of Health showed at least one case where 2 out of 10 commercial analyses of the same sample reported PCB values that were 20-fold different from the median.

The concern about environmental accumulation of PCB's and about possible human health effects led in 1976 to the enactment of Section 6(e) of TSCA. Section 6(e) directs EPA to prescribe PCB marking and disposal requirements; generally bans continued PCB use except in a "totally enclosed manner;" and generally bans PCB manufacture, processing and distribution. The PCB Disposal and Marking Rule and the PCB Ban Rule promulgated by EPA to implement Section 6(e) contain the following major features (58):

- Most items that contain 50 ppm (0.005%) or greater PCB must be labeled.

- All liquids that contain 500 ppm (0.05%) or greater PCB and PCB-containing capacitors with 3 lbs. or more dielectric fluid must be disposed of in an EPA-approved high temperature incinerator.

- All liquids that contain between 50 ppm and 500 ppm PCB must be disposed of in an EPA-approved high temperature incinerator, in a high efficiency boiler or in an EPA-approved chemical waste landfill.

- PCB-containing capacitors with less than 3 lbs. of dielectric fluid may be disposed of as municipal solid waste unless owned by a capacitor manufacturer or manufacturer of items that contain such capacitors (e.g., microwave ovens, electronic equipment and fluorescent light ballasts and fixtures). These manufacturers must dispose of their PCB-containing capacitors in an EPA-approved high-temperature incinerator.

- Waste oil that contains any detectable concentration of PCB's cannot be used as a sealant, coating or dust control agent.

- Most items and liquids that contain 50 ppm or greater PCB and that have been designated for disposal must be stored in compliance with specific requirements.

- PCB's contained in intact, non-leaking capacitors, transformers and electromagnets are being used in a "totally enclosed manner;"* therefore, such capacitors, transformers and electromagnets may remain in service.

- The manufacture, processing, distribution and use of PCB's in concentrations below 50 ppm may continue without restriction*.

*A recent court decision requires EPA to re-examine this determination.

- Eleven uses of PCB's in other than a "totally enclosed manner" (including servicing transformers and electromagnets and PCB use in existing stocks of carbonless copy paper, in pigments and in heat transfer and hydraulic systems) may continue subject to certain conditions and time limits.

The FDA has established tolerances for unavoidable residues of PCB's in several classes of food. Present tolerances are given below (57):

Milk and dairy products	1.5 ppm (fat basis)
Poultry	3 ppm
Eggs	0.3 ppm
Fish and shellfish (edible portion)	5 ppm *

**In 1979 the FDA reduced the tolerance for fish and shellfish to 2 ppm, but stayed the effective date of the 2 ppm tolerance pending resolution of objections.*

Notwithstanding the experience of 50 years usage and the extensive research which has been completed, some questions and uncertainties remain. General Electric and others are continuing research on some of these issues.

The actual PCDF content of PCB's in existing capacitors and transformers as well as in various environmental samples needs to be determined. Based on the reported PCDF content of Aroclors (0-2 ppm), one may postulate that PCDF's will be detected in such minute quantities that they should not be of concern. This postulate needs to be validated by analysis and evaluation, and GE is conducting an analytical research program to make such data available.

A number of medical research programs that will further clarify the possible PCB health effects are continuing. With the cooperation of General Electric, New York State's Department of Health (Dr. Philip R. Taylor) is analyzing further the epidemiology of the GE capacitor worker population, and is extending the research to include reproductive experience. General Electric is continuing medical research with a group of heavily exposed capacitor workers; and some additional observations may become available from the Mt. Sinai School of Medicine's studies of other workers at the same location. The Michigan State Department of Health (Dr. H.E.B. Humphrey) is extending and broadening its study of individuals who have ingested PCB's by eating fish.

Another question concerns industrial exposures of transformer workers. Transformer plants typically used Aroclor 1254 and 1260, usually mixed with chlorobenzenes, for a portion of their production, whereas Aroclor 1260 was not used in capacitors. Few epidemiological studies of transformer workers exposed to PCB's are available. The capacitor worker experience may be relevant, however, as Aroclors 1254 and 1260 contain substantially overlapping though not identical populations of PCB molecules. In addition, capacitor worker blood analyses show retention of the molecules contained in Aroclor 1260.

Lastly, some research programs are being directed at economically effective PCB containment and destruction processes in order to respond more effectively to Federal and State requirements. General Electric is active in some of these programs.

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Human Exposure to Polychlorinated Biphenyls at Toxic Waste Sites: Investigations in the United States

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ABSTRACT. Beginning in 1982, environmental and population data were evaluated from waste sites contaminated with polychlorinated biphenyls (PCBs). Pilot exposure assessment studies were conducted at 12 sites where risks of human exposure were thought to be greatest. Serum PCB levels in persons at highest risk of nonoccupationally related exposures (because of their self-reported frequencies and types of activities in contaminated areas) at 10 sites were within background ranges, even though environmental contamination levels as high as 2.5 parts per billion (ppb) in monitoring well water samples and 330,000 ppb in soil samples were measured. At the 2 remaining sites, elevated serum levels were found in these high-risk persons, which require further evaluation by community surveys. These results illustrate that, despite elevated environmental contaminant levels, unless uptake of chemicals above background exposure levels can be demonstrated, adverse health effects cannot be attributed to waste site chemicals. However, health risks due to background exposure levels, as well as in populations with elevated PCB body burdens need further study.

POLYCHLORINATED BIPHENYLS (PCBs) are lipid-soluble, aromatic compounds comprising 209 possible forms. Each chlorinated structure has several isomers and congeners depending on the number of chlorine atoms in the ortho, meta, or para positions on the two benzene rings. Pollution with PCBs is worldwide; PCBs have been found in soil, water sediments, and freshwater and marine fish, as well as in human adipose tissue and serum.[1]

Laboratory studies have shown an association of PCBs with cancer,[2-5] adverse reproductive outcomes,[6,7] and other organ-specific damage[8,9] in experimental animals. However, the toxicity varies considerably both among congeners within each isomer group and among the different groups; furthermore, different species of animals have widely varying susceptibility to these compounds.[8,9] A major concern is whether environmental contaminations induce adverse human health effects. Although some studies of high-dose occupational exposures have been performed, the health effects in exposed humans, especially at low levels over long time periods, are not as well understood as effects in experimental animals.

Ironically, PCBs may be ideally suited for the study of exposure at toxic waste sites. Analytical measurement of serum PCB levels is a sensitive, stable technique[10] that is performed routinely in selected clinical laboratories through the United States. Serum PCB level is a reliable indicator of body burden, because fat and serum PCB levels equilibrate and remain at a relatively constant ratio for many years.[11,12] Background levels of whole blood and serum PCBs are reasonably well de-

fined by data available for characterized human populations.[7,8] Suitable questionnaires can identify sources of exposure and possible confounding factors. Finally, PCBs are among the most common environmental contaminants at toxic waste sites in the United States; when this study was started, PCBs had been identified at 31% of the sites on the United States Environmental Protection Agency's (EPA) National Priority List of waste sites scheduled for remedial actions.

The purpose of this report is to summarize the results of a series of investigations that was intended to assess the extent and magnitude of human exposure to waste sites contaminated with PCBs throughout the United States.

Materials and methods

To evaluate the potential human health impact posed by PCB-contaminated waste sites, we used a standardized protocol designed for studying exposures and health effects in communities near these sites. The strategy[9] consists of four sequential phases: (1) site evaluation, (2) pilot exposure studies, (3) community surveys, and (4) cohort studies. Results reported herein focus on phase I and II activities under this protocol.

Beginning in 1982, we reviewed site descriptions and environmental sampling data from waste sites which contained PCBs. EPA regional offices had identified 126 such sites, located in 31 of the 50 states, the District of Columbia, and the 4 United States territories. In addition, subsequent to this systematic review of the available environmental sampling data, other PCB-contaminated sites were identified by state environmental agencies or local health departments.

To be selected for detailed study of human exposure (i.e., phase II exposure assessment studies), waste sites had to meet the following criteria:

1. Identified populations at risk of exposure must include
   a. ≥ 100 persons living in areas immediately adjacent to the waste site or
   b. ≥ 50 people known to
      i. have regular contact with contaminated off-site soils, or
      ii. be using contaminated well water for drinking, food preparation, and bathing, or
      iii. regularly eat contaminated native fish, or
      iv. regularly be using contaminated surface waters for recreation.

AND

2. Environmental sampling data for the site had to document on-site PCB contaminations in
   a. soil at levels ≥ 1,000 parts per million (ppm), or
   b. surface/ground water at levels > 1 part per billion (ppb), or
   c. the food chain at levels > 5 ppm

with

unrestricted public access to the site.

OR

3. Environmental sampling data had to document PCB contamination of accessible off-site environmental pathways in
   a. soil at levels > 1,000 ppm, or
   b. surface/ground water at levels > 1 ppb, or
   c. the food chain at levels > 5 ppm.

For each of the waste sites which met these criteria, a pilot exposure study was conducted using standard methods for collection of demographic and exposure data and for collection and laboratory analysis of biological specimens. Studies were conducted by local and state health departments, in consultation with the Centers for Disease Control (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR).

At each selected site, population groups at-risk of exposure in surrounding communities were identified using information obtained from health departments and environmental agencies. Potentially exposed persons were initially contacted by telephone, through citizens' groups, or the news media; using questionnaires, information was obtained from these persons regarding potential exposure through various environmental pathways. On the basis of their responses, individuals who had the highest risk of exposure (i.e., those with the greatest reported frequency and duration of activities which might lead to contact with the contaminated areas) were chosen to participate in the pilot studies. After obtaining informed consent from participants, blood was collected for serum PCB assay. Serum PCB levels were quantitated by standard methods[10] against Aroclor 1260 or 1254 standards. A more complete site-exposure history, demographic information, medical history, relevant occupational history, and a history of non-site-related contact with materials that contain PCBs were also collected. Medical histories included questions about illnesses described in previous human and animal studies as possibly PCB-related, tobacco and alcohol use, and current use of medications.

Results

Twelve sites met the selection criteria for evidence of high risk of human exposure to PCB-contaminated areas, as specified above. The environmental sampling and population distribution data indicated that the likelihood of exposure through inhalation (e.g., breathing volatilization and combustion products from the sites), ingestion (e.g., consumption of contaminated native fish or animal and vegetable products raised in contaminated areas), and/or dermal absorption (e.g., direct contact with PCB-containing transformer fluids and contaminated soil) was high at all these sites (Table 1).

Detailed exposure assessments of potentially affected persons were conducted at these 12 sites; the number of persons who were studied at each of the selected sites ranged between 9 and 114, with a median of 39. As noted in Table 2, no evidence for an increased prevalence of nonoccupationally exposed persons with

Table 1.—Summary of Environmental Sampling Results: PCB-Contaminated Waste Sites at Which Exposure Assessments Were Performed

Location (county and state)	Environmental data (peak PCB concentrations)							
	On-site				Off-site			
	Soil (ppm)	Ground water (ppb)	Surface water (ppb)	Food chain (ppm)	Soil (ppm)	Ground water (ppm)	Surface water (ppb)	Food chain (ppm)
Sebastian, AR	Contaminated oils sprayed directly in residential area.				133,000	NA*	NA	NA
Wayne, GA	3,436	NA	1.5	NA	149	<0.3	8.5 (rainwater runoff)	NA
Monroe, IN (3 sites)	310,000	2.5	18 (water) 520 (sediment)	NA	3,500	ND†	12.2	200 (fish)
Newport, MA	99,000	NA	400 (storm sewer) 22,000 (sediment)	NA	NA	NA	6,100 (water) 66,500 (sediment)	730 (fish)
Norfolk, MA	220,000	NA	NA	NA	3	NA	550,000 (sediment)	NA
Ashtabula, OH	NA	NA	8,390,000 (sludge)	NA	0.1	NA	7.0	1.9 (plants)
Allegheny, PA	32,000	NA	NA	NA	1,106	NA	300,000 (sediment)	NA
Chester, PA	36,000 (soil) 420,000 (work areas)	NA	NA	NA	6,400	ND	86,000 (sediment)	6.6
Pickens, SC	NA	NA	77,200 (sludge)	NA	130	NA	0.9	0.3 (vegetables)
	PCBs discharged directly into area surface waters.						22,080 (sediment)	15 (fish)
Marion, WV	22,226	NA	NA	NA	205	NA	17	1.7 (chicken)

*NA = results not available or samples not collected.
†ND = result below detection levels.

serum PCB levels significantly elevated above background was found in 10 of the 12 sites. In contrast, evidence from two sites (located in Newport County, Massachusetts and Monroe County, Indiana) suggested that environmental contaminations had resulted in human exposures above expected background levels.

On the basis of a preliminary survey in Newport County, Massachusetts, the principal routes of exposure to PCBs had been identified as being direct occupational exposures and the consumption of contaminated fish. Thus, workers at the two local electrical capacitor plants and persons who reportedly ate the most locally caught fish comprised the high-risk group in a pilot exposure assessment conducted at this site.[15] The geometric mean serum PCB level for these 51 persons was 18.1 ppb; of these persons, 35% had serum concentrations ≥ 20 ppb, and 6% had levels ≥ 100 ppb. Among the 42 persons without any occupational exposures, the geometric mean PCB concentration was 12.9 ppb, with 21% having levels ≥ 20 ppb. All of these mean levels and proportions of serum PCB concentrations > 20 ppb are statistically significant above expected background levels.

After conducting an initial screening survey in Monroe County, Indiana, we chose a group of 61 persons who were considered to be at highest risk of exposure because they reported participating most frequently in characteristic activities involving one or more contaminated environmental pathway (e.g., swimming in contaminated surface waters or eating contaminated fish).[16] The geometric mean serum PCB level for this high-risk group was 10.9 ppb with 19.7% of the participants having serum PCB levels ≥ 20 ppb: compared with background levels in representative populations, this was greater than expected ($p < .01$). When we excluded 10 workers with known occupational exposures to PCBs from the analysis of this high-risk cohort, the geometric mean serum PCB level dropped slightly to 9.0 ppb. Among these 51 persons, 9.8% had serum levels ≥ 20 ppb: this, however, was not statistically significantly greater than expected ($p = .12$). In addition, 9 of 55 (16.4%) persons selected randomly from the approximately 1,000 persons living within ½ mile of the three contaminated areas had elevated serum PCB levels, which is statistically different ($p < .01$) from the proportion expected.

Discussion

Results of population-based studies[11-15] have demonstrated that most people without occupational exposures have serum PCB levels in the low parts per billion range, with a median between 5–7 ppb. Approximately 95% of the values are below 20 ppb, and increase with age.[11-15,19,20] For comparison, in a group of 781 Michigan residents with no known exposures, e.g., the mean serum PCB level was 6.0 ppb, 30% had PCB levels ≥ 10 ppb, 7% had levels ≥ 20 ppb, and 2% had levels ≥ 30 ppb.[15]

In 10 of the 12 site-specific investigations conducted under this protocol, no excess proportion of potentially exposed persons was found to have serum PCB levels ≥ 20 ppb attributable to nonoccupational exposures from the sites in spite of high PCB levels in soil or leachate on the sites. As a result, we concluded that there was no need for further studies. The "negative" studies reassured community residents at risk of exposure that they had not absorbed more chemical contaminants than a local or national reference population; however, this reassurance must be qualified by our lack of knowledge of potential long-term health risks that may result from "normal" tissue levels of PCBs.

In the two settings where we found an elevated proportion of unusually exposed persons, further evaluation is required. In Monroe County, Indiana, the findings might be attributable to the historical prevalence of occupationally related exposures. Nevertheless, the findings of the pilot study recommend investigation of the magnitude and extent of exposure and health effects in the residential community through a population-based survey; this study is currently in progress. In Newport County, Massachusetts, where wastes containing PCBs introduced into surface waters contaminated the maritime food chain, another important community survey is nearing completion. Exposures via this route, rather than by direct contact with contaminated soil or water, have been shown to result in especially high serum PCB levels and related health effects.[21-24] The results of the community survey will allow interpretation of the local contamination situation within the context of previous studies of persons exposed to PCBs through the food chain.

Because we did not directly assess human exposure at sites not selected in phase I, we could not evaluate the sensitivity, specificity, and predictive value of the strategy to triage sites for further study. Also, given the relatively small sample sizes in these pilot studies, significant human exposure or increased incidence of health effects attributable to waste site chemicals may not be detected at sites chosen for study. Furthermore, although not studied under this protocol, workers on waste sites and emergency crews which must enter waste disposal sites during fires and explosions may represent a subpopulation at particularly high risk of toxic exposures. Assessment of these groups should be pursued with studies specifically designed to evaluate the unique types, nature, and magnitude of their exposures. For these and other reasons, it would be impru-

Table 2.—Summary of Biological Sampling Results: PCB-Contaminated Waste Sites at Which Exposure Assessments Were Performed

Location (county and state)	PCB measurements in human sera (Quantitated as Aroclor 1260)				Notes
	Number of subjects	Range (ppb)	Geometric mean	% ≤ 20 ppb	
Sebastian, AR	20	2–11	5.8	100	
Wayne, GA	16	3–348	20.9	69	Total high-risk group
	4	3–11	5.1	100	Nonworkers only
Monroe, IN	61	3–75	10.9	80	Total high-risk group
(3 sites)	51	3–51	9.0	90	Nonworkers only
	55	2–47	9.0	84	Subjects selected randomly from at-risk population
Newport, MA	51	2–343	18.1	65	Total high-risk group
	42	2–68	12.9	79	Nonworkers only
Norfolk, MA	90	1–30	4.2	99	Total high-risk group
	89	1–13	4.1	100	Nonworkers only
Ashtabula, OH	59	1–45	4.4	97	Total high-risk group
	57	1–15	4.1	100	Nonworkers only
Allegheny, PA	9	ND*–5	2.7	100	Includes five children
Chester, PA	23	1–79	5.9	91	Total high-risk group
	22	1–31	5.3	95	Nonworkers only
	66	1–24	4.4	97	Subjects selected randomly from at-risk population
Pickens, SC	27	ND–30	2.6	96	Quantitated as Aroclor 1254
Marion, WV	24	1–23	5.0	96	

Note: Non-detectable serum concentrations were assumed to be one-half the detection limit for calculation of geometric means.
*ND = result below detection levels.

dent to infer too broadly from these experiences and conclude that toxic waste disposal sites are not generally hazardous.

Nevertheless, results obtained at sites selected through this triage process may help to direct follow-up epidemiologic studies and in the development of interventions and remedial actions at all waste sites, whether or not they are studied. This is an especially important benefit in local and state health department jurisdictions, where priorities for the use of limited professional and financial resources must be carefully balanced.

In all settings, unless uptake of chemicals occurs, adverse health effects cannot be attributed to waste site chemicals. In general, the experiences related herein reinforce the proposition that public health officials (as well as concerned citizens) need to consider other factors in addition to environmental contamination levels when evaluating human health risks due to chemical waste dump sites. These factors include:

1. the physical and toxic characteristics of waste site chemicals;
2. the volatility and spread of waste site chemicals via different environmental pathways;
3. access to and frequency, duration, and type of use of contaminated areas;
4. absorption potentials of these chemicals in biological systems; and
5. the presence of human populations at risk of exposure, especially sensitive subpopulations (such as children and pregnant or lactating women).

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Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

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FOLLOW-UP STUDY OF CAPACITOR WORKERS EXPOSED TO POLYCHLORINATED BIPHENYLS (PCBs)

by

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SUMMARY

A population of capacitor workers exposed to PCBs, studied previously in 1976 and 1979, was reexamined in 1983. Mean workplace area air levels of PCBs had declined to 16 $\mu g/m^3$ by 1983. Although PCB body burdens of the higher PCB congeners (Aroclor 1260) have remained relatively constant, lower PCB congener body burden dropped, probably as a consequence of metabolic clearance. Serum PCB concentrations, calculated on the basis of total serum neutral lipids, were not statistically associated (<5%) with 23 biochemical or 12 hematological variables measured except for the percentage of basophils. The significant intervening variables — which included average age of the population (49.5 years), sex, obesity, and alcohol consumption — accounted for many of the laboratory findings outside the normal ranges. No statistically significant associations were found of serum PCB levels with blood pressure.

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KEY WORDS: polychlorinated biphenyls (PCBs), capacitor workers, occupational exposure, health effects

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FOLLOW-UP STUDY OF CAPACITOR WORKERS EXPOSED TO POLYCHLORINATED BIPHENYLS (PCBs)

R.W. Lawton, MD; M.R. Ross, RN, COHN; and J. Feingold, MD

INTRODUCTION

Polychlorinated biphenyls (PCBs) were the only chemicals singled out by name for special attention in a ban on the substance by the Toxic Substances Control Act (TSCA) of 1976. This action arose from a series of events beginning with the observation of environmental persistence by Jensen (1) in 1966, followed by an outbreak of apparent PCB poisoning in Japan in 1968 (2). This episode (Yusho disease) is now known to have resulted from rice oil contaminated by thermally degraded PCBs from a leaking heat exchanger. The oxidative degradation of the PCBs resulted in the production of polychlorinated dibenzofurans (PCDFs) (3). A similar PCDF poisoning episode subsequently occurred in Taiwan (4). Some sporadic reports of chloracne thought to be related to PCBs appear in retrospect to be caused either by PCB which had been contaminated in production (5) or by thermally degraded PCBs (6,7). The final event leading to the PCB ban was the demonstration by Kimbrough et al. (8,9,10,11) of adenofibrosis, hepatoma formation, and hepatic carcinoma in rats with massive doses of the largely non-metabolizable Aroclors (1254 and 1260). These findings have recently been confirmed in PCDF-free PCBs by Schaeffer et al. (12) who observed that hepatic carcinogenicity was only associated with the highly chlorinated isomers and was accompanied by a suppression of the spontaneous incidence of tumors in other organs and tissues.

Historically, PCBs have been considered a relatively safe substance. Following the commercial introduction of PCBs in the 1930s, their production in the U.S. through 1975 totaled about 1.4 billion pounds (13). Air standards controlling PCB use in the workplace were based for many years on the animal studies of Drinker et al. (14) that in 1937 indicated relatively low toxicity. Drinker was the first to clearly separate the effects of PCBs from those of the chloronaphthalenes (15).

After environmental persistence of PCBs was demonstrated by Jensen (1), Monsanto (the principal U.S. manufacturer of PCBs, produced under the trade name Aroclor) responded by making available in 1970 a redistillation product, Aroclor 1016. This product was for use in closed systems (capacitors and transformers), replacing Aroclors 1254 and 1242 which had been in use.

The Aroclor 1016 product consisted of isomers all with less than five chlorine atoms per molecule, eliminating the apparently persistent higher congeners. Enhanced biodegradation of Aroclor 1016 was shown by diminished accumulation and by rapid and more complete depletion in rat feeding experiments (16). The clearance mechanism was found to involve mixed function oxidase induction (17). In the environment, aerobic bacteria have been shown to degrade many of the lower PCB congeners by dioxygenase induction (18), and anaerobic bacteria appear capable of dechlorinating many of the higher chlorinated congeners (19).

The effect of the Yusho disease incident on PCB regulation may have been quite different if the role of PCDFs had been discovered earlier. The identification of PCDFs as the toxic agent in Yusho disease was not made until 8 years after the event. It is now known that U.S. commercial PCBs contained approximately 1 to 2 ppm of PCDFs (Aroclor 1016 contained negligible amounts of PCDFs). In Yusho, the concentration of PCDFs in the PCBs present in rice oil was subsequently found to be 0.9%, and in blood samples of Taiwanese patients, PCDF concentrations varied from 24 to 100 ppt. In experiments on monkeys, PCDFs preferentially accumulated in the liver and were 2500 times more powerful as a chloracnegen than PCBs (23). An entire issue of the American Journal of Industrial Medicine (Vol. 5, No. 1/2, 1984) reviews the current status of the Japanese and Taiwanese events, and clearly indict PCDFs rather than PCBs as the causative agent.

Another factor that ultimately affected PCB regulation is the fact that many of the cross-sectional human studies of occupational or environmental exposure to PCBs have been largely descriptive in nature (24-28). Where statistical analysis has been performed (29-33), the correlations reported in earlier studies of serum levels of triglycerides, cholesterol, and some liver enzymes with the gross serum PCB level (serum weight basis) appear now to be related to the partitioning behavior of PCBs in the serum lipids (33, 34). In particular, the studies of Chase et al. (32) showed that the correlations of the gross serum PCB levels with the serum triglycerides, cholesterol, and glutamic oxalacetic transaminase disappeared when the adipose tissue PCB level was used as the independent variable.

We have reported results in capacitor workers in which the serum PCB concentration was calculated in terms of the total serum neutral lipid (33) and have found that the associations with serum triglycerides and cholesterol were fully accounted for by such partitioning. Residual associations with serum γ-glutamyl transpeptidase and bilirubins were found during high active exposure to Aroclor 1016 in 1976, which we interpreted as evidence for glucuronyl transferase induction, elevated glucuronidation, and accelerated hepatic clearance. Such statistical relations had largely disappeared in the results of the 1979 study.

The present study is an analysis of clinical cross-sectional data obtained in 1983 on the same capacitor worker population 6.5 years after the cessation of PCB use. This study provides additional significant longitudinal information relating to the longer term effects of their occupational exposure.

MATERIALS AND METHODS

Study Population

The study population was selected in early 1976 to include all those workers with occupational exposure to PCBs, about 10% of the work force of two capacitor manufacturing plants in upper New York State. Criteria for selection and exposure classification at this time resulted in three groups:

- Jobs requiring prolonged direct dermal contact in areas with high air levels, such as handling and sealing wet capacitors and capacitor salvage and repair (high exposure)

- Maintenance men, foremen, and engineers whose duties generally involved brief high exposure and contact (medium exposure)
- Workers whose jobs did not require direct contact but who were located at the periphery of zones with high air levels (low exposure)

Initially, 194 workers participated on a voluntary basis. The population was restudied in 1979, and the 1976 and 1979 data - together with a further description of exposure conditions - are presented elsewhere (33).

For the present study (late 1983) the population was contacted by letter and telephone and again invited to participate. Because of retirement, separation, refusal, or death only 154 workers were subsequently examined. Some workers refused portions of the examination so that complete data were obtained on only 146 workers (115 males, 31 females). Compared to those with complete data in 1976 (176 workers) participation was 83%.

Clinical Measurements

The clinical examination consisted of an updated medical history, physical examination by the plant physician, ECG, chest x-ray, spirometry, 23 biochemical measurements, CBC and differential, and a routine urinalysis. Body weight was measured in light indoor clothing, and height measured without shoes. A single systolic and diastolic blood pressure was measured in the seated position to the nearest 5 mm Hg. Participants were instructed to be fasting for the preceding 12-hour period with water ad libitum. Only one non-fasting worker was identified.

The updated medical history was directed primarily to the description of smoking habits, alcohol consumption, and the use of medications. Smoking histories had not changed since the previous examination. Smokers and ex-smokers made up 71.9% of the study group. Forty-two percent of the population consumed alcohol on a regular basis, primarily in the form of beer. We found it convenient to describe consumption in terms of a "six-pack per week" scale (Figure 1). Two workers admitted consumption in excess of four six-packs per week.

Fifty-six workers reported the use of medications consisting of 42 generic drugs (Table 1). Thirteen workers used analgesics, antihistamines, and antacids. Seventeen reported a physician's diagnosis of hypertension, and 26 used antihypertensives and other cardiovascular drugs (diuretics, beta-blockers). Also reported were antiarthritics and gout medications (10), antibacterial medications (2), and steroids (3). Five workers took diazepam, and one phenytoin.

From a review of the literature, from structural analogy, and from half-life considerations, we classified 20 drugs with respect to their mixed function oxidase activity. There were 22 drugs for which little information could be found. [These 22 drugs (Table 1) were classified as having no effects.] Some other known effects are also relevant to this study: Propranolol inhibits its own metabolism but not in the presence of some other drugs (34). Insulin lack depresses drug metabolic activity, but thyroid hormone may increase or decrease drug metabolism

ciencies in riboflavin (36), vitamin C (37), and vitamin E (38) decrease drug oxidation.

In order to determine the PCB body burden, we calculated the total body fat from the weight-height regression equations of Hume and Weyers (39). These equations, based on total body water determinations, depend upon the assumption of adequate body hydration. We used the urinary specific gravity as the measure of hydration in these studies and found it to be equivalent to the calculated serum osmolality derived from conventional assumptions (40). Two other methods were considered for determining total body fat: the model of Moore et al. and the Benn procedure (42). The Moore total fat model (41) (regression equations in weight and age) may be a more desirable clinical model but presents problems in age colinearity in regression. The Hume and Weyers model used in our study is more allied to the body mass index. Satisfactory body mass indices were calculated for the population using the Benn procedure only when unusual height-for-weight values were removed.

Serum PCB Measurements

Packed column gas chromatography was conducted on a serum sample from each worker by Hazleton Laboratories America Inc., Madison, Wisconsin, by methods previously described (43). Serum PCB levels were estimated using the standard Aroclors (1242, 1254, and 1260) and the sum of selected peak heights method of quantitation to provide consistent methodology over the period from 1976 through 1983. This method of quantitation evaluates the serum level in terms of the most persistent peaks and overestimates the actual PCBs present. Although methods of adjustment of the data have been proposed (43), for the purpose of multiple regression these additional calculations altered the intercepts but not the coefficients in the regression equations, and have therefore been omitted. Repetitive measurements on a serum pool and serial dilution experiments have indicated a 95% prediction interval for the gross serum PCB level of approximately ±50% for these PCB measurements.

After packed column chromatography was completed, the extracted samples were returned to our laboratory for capillary gas chromatography. After additional cleanup by an H_2SO_4 wash, the analysis was performed using procedures described elsewhere (19). These procedures have resulted in the identification of 130 isomer peaks in standard chromatograms. Peaks were numbered according to the system of Ballschmiter and Zell (44) and their identities assigned from a number of sources (45, 46), including recent GC-MS data (R. Wagner, J. Carnahan: personal communication).

PCBs are lyophilic and are dissolved and distributed in serum primarily in the lipoproteins (47, 48). It has been estimated that the lipid phase for PCB partitioning in serum can be approximated by the total serum neutral lipids (49). At equilibrium the PCB concentration in this serum lipid phase was found to be substantially equivalent to its concentration in adipose tissue lipids. Serum cholesterol lipids (comprising free plus esterified cholesterol) were estimated from normal values (50) as 1.5 times the clinical total cholesterol, and the total serum neutral lipids given as the sum of the serum cholesterol lipids and the clinical serum triglycerides. The PCB body burden was calculated as the product of the PCB concentration in total serum neutral lipids

and the total body fat.

In multiple regression studies, we evaluated two measures of exposure derived from the PCB measurements: the gross serum PCB level reported by the laboratory as ppb on a serum weight basis, and the serum lipid PCB value in ppm, the pharmacologically active concentration (51). An additional measure of exposure was derived from the exposure categories assigned in 1976 (Table 2).

Statistical Analysis

Statistical analyses were performed on a Honeywell 600/6000 computer, using STATPAC (52), a versatile general statistical package, which provided distribution plotting, multiple and stepwise linear regressions, and analysis of variance. The 23 biochemical and 12 hematological measurements were used as dependent variables in multiple backward-stepwise regressions in the presence of selected confounders, and each was examined for statistical associations with each of the three measures of PCB exposure. The criterion for statistical significance was $F_{(1-\alpha)}\ 0.95 = 3.9$, so that the 95% confidence interval for a significance coefficient did not include zero. The results are given as partial correlations that were significant at approximately 0.165. We selected the backward step procedure as the best method for managing the multiple colinearities in the data.

The dependent variables were examined for their distributions using cumulative percentage plotting and were log-transformed as required. Final distribution selections were made on the basis of residual plots at the end of the stepwise regressions. Outliers were not removed. All PCB measures were log-transformed and produced a linear distribution on cummulative percentage coordinates. Other log transformations included serum triglycerides, the liver enzymes (GPT, GOT, and GGTP), total bilirubin, serum globulin, blood glucose, BUN, BUN/creatinine ratio, the white blood count, eosinphils, and the MCHC (see Table 6 for abbreviations).

In the statistical analysis we considered a variety of independent variables as confounders (Table 2). These were screened by regression using gross serum PCB levels as the dependent variable. For this analysis we used the 1976 relative exposure estimate based on analysis of the individual job activities, as well as plant locations at that time. Service time was used in lieu of age; the latter was used for the analysis of clinical variables (age and service time covaried: $R = 0.74$). Serum albumin was evaluated as an independent variable only in the PCB-dependent regressions.

Two classifications of job status were used in order to test the effects of the duration of separation or retirement: one involved only workers retired prior to 1979; the other involved all workers retired prior to this study. Because all salaried workers were male, and the females worked primarily at only one plant, both the salaried/hourly and plant location classifications covaried with sex ($R = 0.25$ and 0.35, respectively). Certain workers with intercurrent illnesses that we expected to influence the results - e.g., diabetics, ex-alcoholics, post-surgery patients, etc. - were identified and coded.

RESULTS

PCB Exposure

Over the course of our observations, mean PCB air levels in capacitor manufacturing areas fell from nearly 700 $\mu g/m^3$ during active PCB use in 1976 to around 16 $\mu g/m^3$ shortly before the present study (Figure 1). This declining exposure was associated with extensive clearance of the lower PCB homologs as measured by the gross serum levels (packed column GC) of Aroclor 1242. Figure 2 indicates a decline in the mean body burden of lower chlorinated congeners from 5.6 to 0.52 g over the 8-year period, with a somewhat slower rate of decline in the females (triangles). In contrast, body burdens of the higher chlorinated congeners (quantitated as Aroclor 1260) have been relatively constant (approximately 0.13 g). Aroclor 1254 burdens have declined slowly as a consequence of the composition of this Aroclor, which overlaps both Aroclor 1242 and 1260.

Capillary gas chromatography was performed on a sample of 10 male workers with relatively normal serum lipid levels (mean serum triglycerides = 92.9 mg/dL; mean serum cholesterol = 174.1 mg/dL). Identification and average composition of the most persistent isomers of the residual serum PCBs are given in Table 3. These estimates of persistence are equivalent to those reported by Wolff et al. (59). The mean values are also compared to the relative fraction of these isomers in the Aroclor 1242 and 1260 standards. IUPAC No. 180, a prominent heptachlorobiphenyl in Aroclor 1260, has also been included. We found that the three major residual peaks of Aroclor 1242 and the six of Aroclor 1260 accounted for 62.5% and 80.4% of the compositions in serum compared to 10.4% and 55.3% in the standards. These persistent peaks in the capillary chromatograms represent the measured peaks in packed column analysis using the sum of the peak heights method of quantitation. An approximate adjustment for the packed column data of 1983 (Figure 2, Table 4) using these relative compositions indicates multipliers of 0.166 and 0.688 for Aroclor 1242 and 1260, respectively, to derive actual serum levels and body burdens.

The most persistent chemical structure appears to involve the 2,4,5 configuration. Isomers reported as toxic in animals (3,4,5,3',4'; 3,4,5,3',4',5') were not found. Small peaks associated with 3,4,4' and 3,4,3',4' (also toxic in animals) were identified in these human samples. These peaks accounted for only 0.5% of the serum composition but contained other coeluting isomers.

In Table 4, we contrast the gross serum PCB levels (packed column method) found in various groups of workers compared to the study population. Clerical workers employed an average of 24 years at the site showed elevated levels of the lower homologs as the result of the general elevation of air levels within and outside the plants. New employees (average service time of 2 years) showed elevations thought to be a consequence of residual plant air levels since the PCB ban. Laboratory workers at another facility actively engaged in PCB research showed elevations of both lower and higher homologs. For the population of this study (1983), lower and higher gross homolog levels were 18 and 3.4 times the nonplant controls, the former having declined 92% since 1976.

Serum PCB levels were conditioned by a variety of factors. We performed multiple linear backward step regressions in which the gross serum PCB level was taken as the dependent variable with the 21 independent variables shown in Table 2. Table 5 shows the significant independent variables as partial correlations for the three examinations (1976, 1979, and 1983) using Aroclor 1242 for a population (136) having complete data (1976 N = 135). The asterisks indicate significant variables for the higher homologs (Aroclor 1260).

Exposure, as measured by the exposure category, was the primary determinant of Aroclor 1242 level. Service time was the major correlate for Aroclor 1260 (partial R = 0.53). Whether the worker was fasting or non-fasting (1976) was significant only for the lower homologs. Serum lipid levels were significant in all cases as a consequence of the physical distribution of PCBs in the lipoproteins. In 1983, an inverse association with serum albumin was found in all cases. There was a positive association with body fat for both lower and higher homologs in 1979, but only for the lower homologs in 1983. Because all the salaried workers were male, sex and the hourly/salaried variables were redundant. Serum PCB levels were inversely associated with smoking in the case of the lower homologs. We found no dependence of serum PCB levels on the hepatic enzyme levels, alcohol consumption, or medication use.

Biochemical and Hematological Findings

Means, standard deviations, and ranges of the biochemical and hematological measurements made on the study population in 1983 were compiled. Of more interest were the number of values that either exceeded or were less than the age- and sex-adjusted standards of the laboratory, which are shown in Table 6. We note elevated serum triglyceride, cholesterol, GPT and GGTP levels. Elevated levels of other enzymes (serum GOT, alkaline phosphase, and LDH) were not observed. There were elevations in blood glucose (five workers were known diabetics) and uric acid. Although albumin and globulin levels were normal, the albumin-globulin ratio was elevated in 21 cases. The BUN/creatinine ratio was elevated in 11 cases. Elevations in serum potassium and chloride levels were found in males.

In hematology we found reduced red cell counts among males with elevated MCV and MCH values. White cell counts were low in 16 cases, with a relative neutropenia and elevated lymphocytes, monocytes, and eosinophils. Urinary specific gravity averaged 1.022 ± 0.006. Calculated body fat for males and females averaged 21.4 ± 7.0 and 22.1 ± 9.5 kg, respectively; as a percentage of body weight the equivalent values were 25.3% ± 4.7% and 32.3% ± 8.5%.

Regression and Results

Associations with PCBs

The biochemical and hematological variables were examined as dependent variables in multiple linear backward step regression. Each variable was examined for its association with the serum PCB level as an independent variable in individual analyses for the gross serum level and the serum lipid level in the presence of selected confounders. The results are given in Table 7 as partial correlations for those cases

where a statistically significant association between a PCB measure and the clinical variable was observed. The data of Table 7 are for Aroclor 1242 (lower homologs) and Aroclor 1260 (higher homologs). No additional associations were found with Aroclor 1254 and no associations found using the 1976 exposure category when either were used as the independent exposure variable.

For both the lower and the higher homolog gross serum level, significant associations existed with both the triglycerides and cholesterol. Conversion to the serum lipid values indicated no residual associations not accounted for by the PCB distributions in the total neutral lipids. In the 105 regressions using the PCB concentration in serum total neutral lipids, only a single significant association was found: that between the lower homolog values and the percentage of basophils. However, this association depended upon the classification of the job status (working/separated). Removal of job status as an independent variable, or the inclusion of recent retirees, removed the serum lipid PCB-association indicating colinearity of the PCB level and job status.

The absence of significant associations with serum bilirubin levels and GGTP and the serum lipid PCB level observed in 1976 and 1979 (2) were apparently not due to the addition of alcohol consumption and medication use as independent variables in this study. Removal of these latter variables from the present regression did not influence the result.

We also investigated the statistical associations of PCB levels with the systolic and diastolic blood pressure used as dependent variables (Table 8). No measure of PCBs was significantly associated with either pressure. Both systolic and diastolic pressures were positively associated with obesity and the use of antihypertensive medications. Systolic pressures were higher in those reporting use of tranquilizers (MED), and diastolic pressures were higher in those reporting a physician's diagnosis of hypertension.

Associations with Confounders

The interrelations of the independent variables with the clinical measurements were dominated by the age and sex differences and by alcohol consumption and obesity. We noted that 12 clinical variables had no significant independent variable other than age or sex, including serum cholesterol, SGOT, SGPT, and LDH, and that 13 variables were a significant function of age. At the time of the present study the average population age was 49.5 years. Obesity (body fat) was significantly associated with elevated serum triglycerides, GGTP, blood glucose, and uric acid. Cholesterol levels were elevated primarily as a function of age. Diabetics and ex-alcoholics tended to have higher triglycerides, uric acids and serum phosphate levels. Alcohol consumption influenced the levels of GGTP and total bilirubin and was associated with a macrocytosis (elevated MCV) and a decreased red count. We observed positive associations of MFO inducers with the BUN and the BUN/creatinine ratio and an inverse association with serum potassium which appeared most likely to be related to the use of non-steroidal antiinflammatory drugs (60) and diuretics complicated by the use of potassium supplements in some individuals. We calculated the serum osmolarity for the members of

the population and found the mean to be 297.1 ± 4.7 mOsm/kg water (range: 282-310), which was elevated over the expected range of 290-295. Serum osmolarity was found to substitute for urinary specific gravity as an independent variable in multiple regression.

DISCUSSION

A group of capacitor workers directly exposed to PCBs has been followed with clinical examinations and serum PCB levels over a period of nearly 8 years. At the time of the present study, 6.5 years had elapsed since the cessation of PCB use. Participation in the present study was voluntary, and only 83% of the 1979 population was recovered so that individuals with adverse effects could have been removed by the self-selection process. However, the log-normal distributions of the population serum PCB levels and the normal distribution of the residuals following multiple stepwise regression which we observed suggest that the statistical requirements for a dose-response relation, if present, had been met. Since the PCB ban, the PCB air levels in the workplace have continuously declined, resulting in an average residual area air level just prior to the present study of only 16 $\mu g/m^3$ (Figure 2). We found this decline in exposure to be accompanied by a dramatic reduction in calculated PCB body burdens among these workers as measured by packed column chromatography in terms of Aroclor 1242 (Figure 3). The higher chlorinated species (calculated as Aroclor 1260) showed relatively constant values. Aroclor 1254 fell in between as a consequence of its overlapping isomer composition with both Aroclor 1242 and 1260. Aroclor 1260 was never used in capacitor manufacturing; the levels for that substance represent either prior exposures to Aroclor 1254 (used between 1946 and 1954), the gradual accumulation of traces of the higher chlorinated isomers found in Aroclor 1242, the primary constituents of the dielectric fluid used between 1954 and 1970, or exposure to PCBs in the environment, which tend to be the highly chlorinated species.

PCB body burdens were calculated from the serum PCB levels that were estimated by the sum of the selected peak heights method of quantitation. With the same methodology, a comparison of gross serum PCB levels with other small worker populations (Table 4) indicated not only the magnitude of the exposure in the study population, but the generally elevated levels of the lower homologs in long-service employees and their accumulation in new employees as the result of exposure to the plant residuals. Such levels in the general plant population precluded the use of an in-plant control group for the conduct of this study. The quantitation methodology, however, overstated the actual PCB concentration present. The selected peaks for measurement represented the most persistent ones. This problem was previously studied in a sample of workers with high PCB levels, and these persistent peaks were found to provide approximately 25% and 70% of the Aroclor 1242 and 1260 compositions, respectively (43). No data, however, are available for the conversion factors at low serum levels.

Capillary gas chromatography results on the sera of a representative sample of workers in the study population should be considered preliminary and were complicated by sample contamination. However, they indicated the nature and magnitude of the PCB clearance process and approximated the present residual serum PCB composition. The residual isomer composition (Table 3) provided the PCB concentration to which any

present biochemical or hematological findings should be ascribed. Isomers for which toxic properties have been indicated in experimental animals were not identified.

As we have noted elsewhere (49) and have shown in Table 5, the gross serum PCB concentration is strongly dependent on the serum lipid concentration, which follows from the equilibrium distribution of PCBs throughout the body fat. Conversion to the serum lipid PCB concentration (total serum neutral lipid basis) fully accounts for the observed associations between the gross serum PCB levels and the serum triglycerides and cholesterol levels measured clinically (Table 7). By analogy with other fat-soluble agents, the pharmacological activity of PCBs is most effectively represented by its concentration in lipids (49,51). These assertions are at variance with the conclusions of others who have tended to ascribe any observed hyperlipidemia in exposed populations to the biological effects of PCBs rather than the partitioning behavior of PCBs in serum lipids.

Multiple step-wise regressions with both serum triglycerides and cholesterol as independent variables always resulted in the selection of serum triglycerides as the significant association with the gross serum PCB level, although serum cholesterol, when used alone, had an equally strong association with gross serum PCBs. This problem in colinearity, which has been noted by Kreiss et al. (30), is resolved by the use of the total serum neutral lipids as the dependent variable (Table 5). The preferential selection of the serum triglycerides may be based on solubility considerations. The inverse association with serum albumin presumably reflects the protein binding observed with other organochlorides (53), which has now appeared as a significant partitioning variable following clearance of the metabolizable isomers. We note also the positive association of gross serum PCB levels with amount of body fat, suggesting that in the more obese workers, PCBs were less readily mobilized and equilibrium not assured. However, our observations on changes in serum lipids in the absence of substantial weight loss (49), the proportionality of the lipid content of organs and tissues and their PCB concentrations (47), and studies during cachexia and starvation (54,55) all support the qualitative if not quantitative thesis of PCB partitioning in serum and tissue lipids.

Gross serum PCB levels were also found to be strongly and inversely dependent on smoking (Table 5). This association was only found for the lower PCB congeners (Aroclor 1242) and is thought to be directly related to the induction of mixed function oxidases by both nicotine and the various constituents of cigarette smoke. Studies by McLemore et al. (56, 57) on alveolar macrophages, peripheral lymphocytes, and pulmonary biopsy tissue have documented in detail MFO induction by cigarette smoke. Although alcohol consumption and medication use appeared as significant independent variables in relation to some clinical parameters, neither were significantly associated with serum PCB levels.

Using the serum lipid PCB concentration as the independent exposure variable, we found virtually no statistically significant association of any Aroclor with the measured biochemical and hematological variables (with the single exception of the percentage of basophils and Aroclor 1242), despite the clinical values reported outside the normal laboratory ranges (Table 6). In addition, no significant associations were found with the 1976 exposure category, an estimate of prior expo-

sure in these workers. One effect of the conversion of the gross serum concentration to the serum lipid concentration was to eliminate associations based solely on covariance with the serum lipid concentration (33). Such covariance may have accounted for the gross serum PCB associations with some liver enzymes observed by others. These 1983 results contrast with the findings in 1976 during active exposure where the central observations (a positive association of serum lipid PCBs with serum GGTP and an inverse association with the serum bilirubin) appeared to reflect microsomal enzyme induction, enhanced glucuronide-conjugating capacity, and accelerated hepatic elimination. Such effects were much diminished in 1979 and were absent in the current data, suggesting that the clearance of the most easily metabolized lower PCB congeners was substantially complete.

We were unable to confirm the association between PCB levels and either the systolic or diastolic blood pressure found by Kreiss et al. (30). Although blood pressure measurements consisted of one casual observation, we found strong associations for both with obesity and the use of hypertensive medications. Systolic blood pressure was related to the use of MFO inducers, presumably tranquilizers such as diazepam. Diastolic blood pressures were associated with a reported physician's diagnosis of hypertension and were lower in smokers and ex-smokers.

The occurrence of changes in the WBC and differential merits attention (Table 6). In Yusho a slight leukocytosis (2) or elevated WBC (4) was found. In occupational PCB exposures, normal hemoglobins and hematocrits (27,31) and normal RBC (27) were reported. WBC differentials were either not measured (26) or not reported (24,27,29,31,32). Maroni et al. (28) reported normal WBCs and differentials. Because no statistically significant associations with serum lipid PCB levels were found, these changes could represent effects of other exposures in the workplace, perhaps trichlorobenzene (TCB, primarily the 1:2:4 isomer), which was used as a constituent of the substitute dielectric between 1977 and 1983. In 15 exposed workers at these plants, serum TCB levels ranged from 0.55 to 6.75 ppb, whereas in 16 of 18 nonexposed workers, the levels were ≤0.4 ppb, the detection limit. However, no changes in hemoglobins or hemocrits were observed in rats fed 10 to 40 mg/kg/day TCB for 90 days (58) where it was shown to be a potent MFO inducer. The clinical findings of neutropenia with elevated lymphocytes and monocytes together with a reduced white count and the percentage of basophils remains unexplained.

Given the intense exposure and the massive clearance of PCBs in this population in the past, the relative absence of statistical associations of clinical variables with serum PCB levels at present is noteworthy. These capacitor plants consumed about 15% of the U.S. PCB production (13), and the study population probably represents one of the most highly exposed populations that will ever be encountered. The clinical findings of hyperlipidemia with liver enzyme and uric acid elevations appear to relate primarily to age, obesity, smoking, and alcohol consumption. Additional studies of the hematological findings appear warranted following the phase-out of trichlorobenzene that was completed in 1983.

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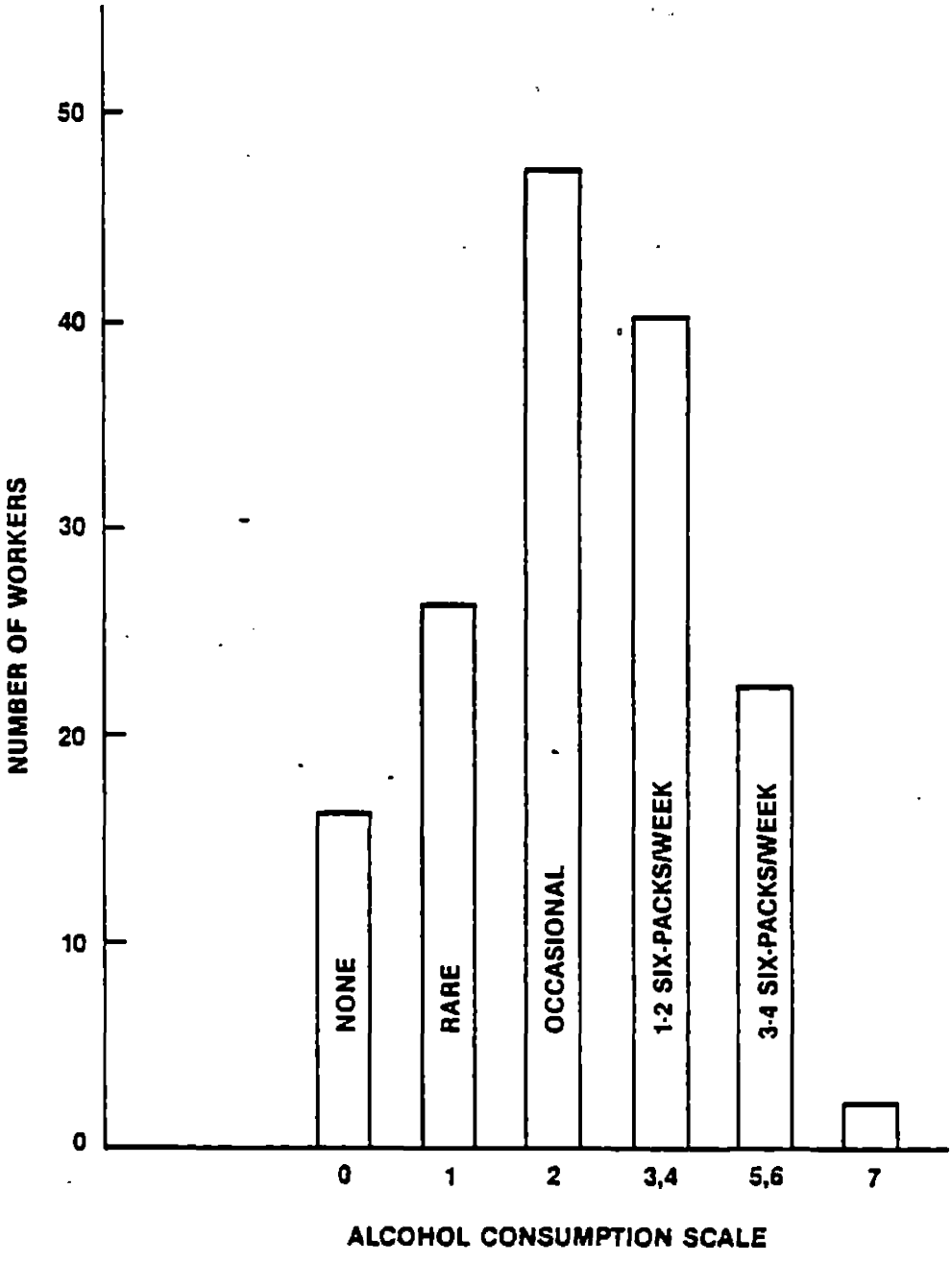

Figure 1. Alcohol consumption scale. Major consumption was beer reported as six-packs per week. Scale (0–7) used as a dummy variable in regression analysis.

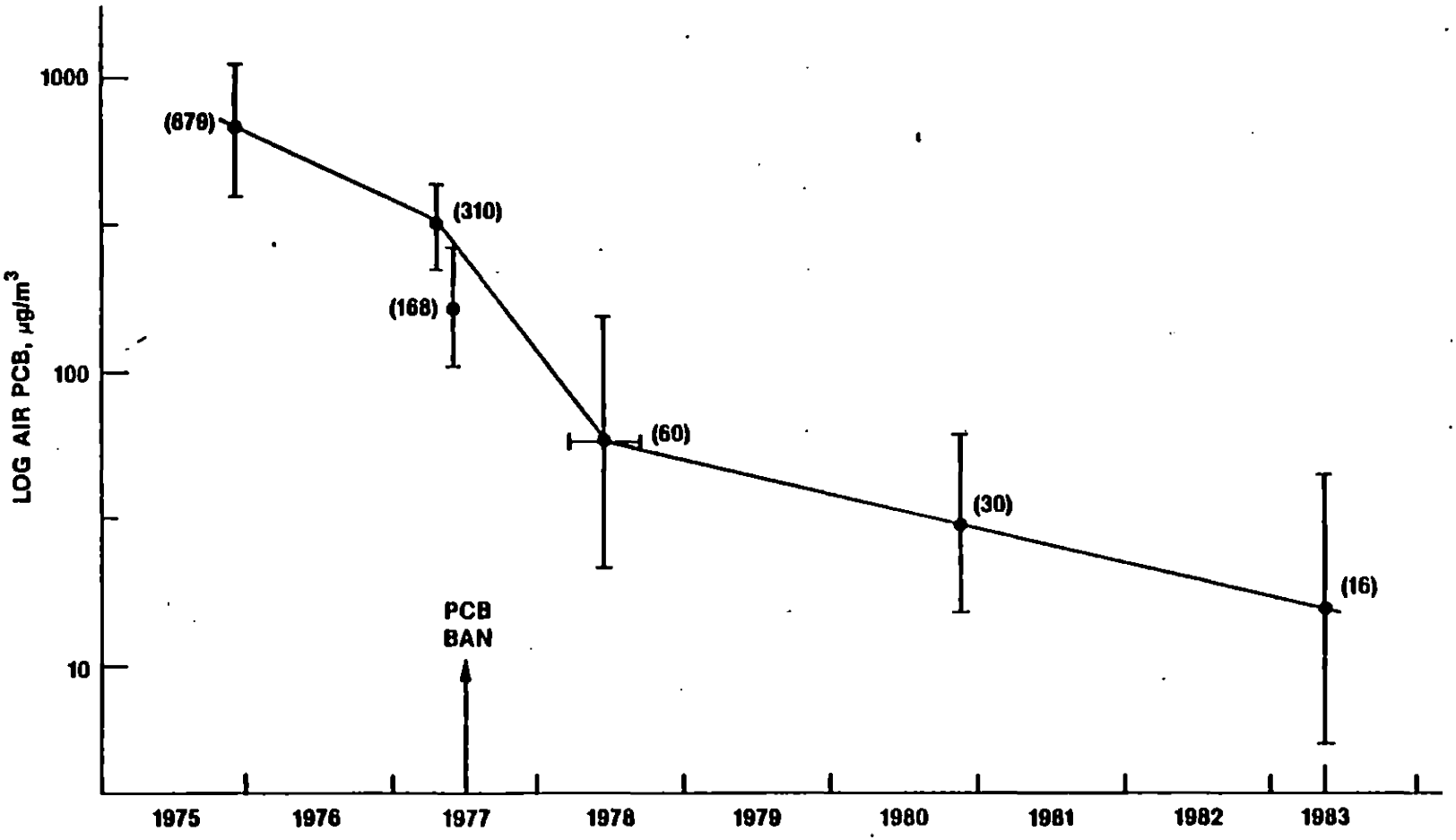

Figure 2. Area air levels (as Aroclor 1242) in workplace (log $\mu g/m^3$ ± 1 SD) in relation to PCB ban. Geometric means are given in parentheses. TWA values in 1977 (geometric mean = 168 $\mu g/m^3$) measured by NIOSH. Values in 1978 measured over a number of months.

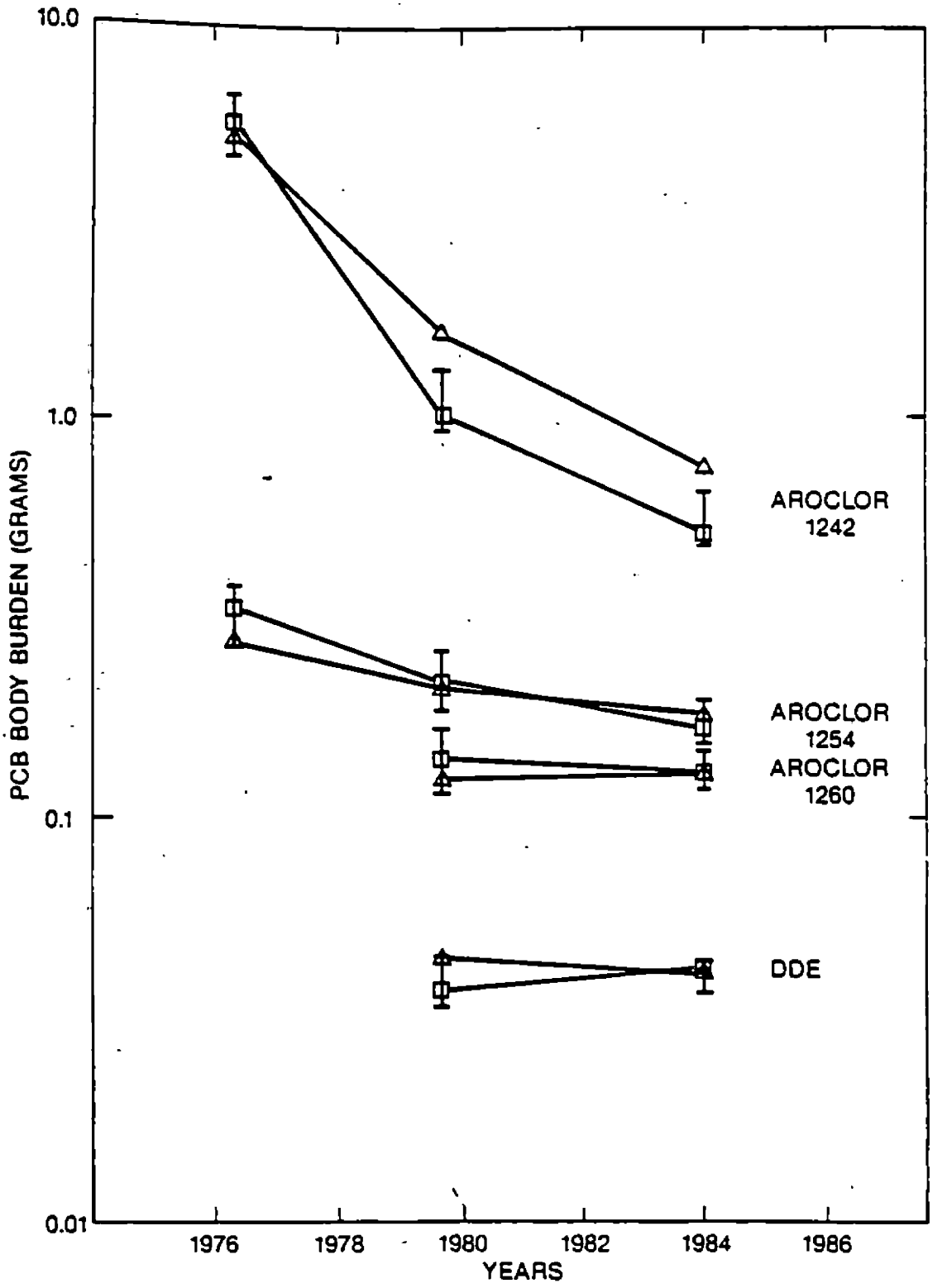

Figure 3. PCB body burdens in capacitor worker population calculated as the product of the serum PCB concentration in total serum neutral lipids (ppm) and the total body fat (kg) given as the 95% confidence interval of the population mean (bar). Males = square; females = triangles.

Table 1

CLASSIFICATION OF MEDICATION USE (GENERIC NAMES)

Reported by Study Population According to Mixed Function Oxidase (MFO) Induction or Depression; MFO Activity Estimated from Literature, Structural Analogy, and Half-Times; No Information Available on 22 Drugs

Weak Depressant	No Information
Butalbital*	Acetaminophen
Cimetidine*	Allopurinol
Indomethacin*	Cyclandelate
Quinine*	Ethoheptazine
Spironolactone	Hydrochlorothiazide
	Hydroflumethiazide
No Effect	Insulin
	Metolazine
Acetylsalicic Acid	Methylchlothiazide
Ibuprofen†	Methyldopa
Phenacetin*	Nitroglycerin
	Penicillin
Weak Inducer	Pentaerythritol Tetranitrate
Brompheniramine*	Phenylpropanolamine
Caffeine	Piroxican
Chlorpheniramine*	Prozosin HCl
Chlorpropamide*	Propranolol
Cyclobenzaprine HCl*	Reserpine
Cortisone	Sulfadiazine
Diphenhydramine	Thyroid
Hydroxyzine*	Vitamins
Meprobamate	Warfarin
Strong Inducer	
Diazepam	
Phenytoin	

*Structural analogy
†PDR

Table 2

CANDIDATE CONFOUNDING VARIABLES AND COMPUTER CODING

Variables Screened for Associations with Serum PCB Levels (Table 5)

	Abbreviation	Measure
PCB Exposure		
Gross serum PCB	GSPCB	Reported value (ppb)
Serum lipid PCB	SLPCB	Calculated value (ppm)
PCB body burden	BBPCB	Calculated value (g)
Exposure category	EXE	Code: 0 = low exp.; 1 = med. exp.; 2 = high exp.
Serum Lipids		
Triglycerides	TRI	Clinical value
Cholesterol	Chol	Clinical value
Total neutral lipids	TNL	Calculated value (TRI + 1.5 Chol)
Serum Albumin	Alb	Clinical value
Body Fat	Fat	Calculated value (Hume and Weyers)
Body Hydration	SPG	Urinary sp. gravity Clinical value
Time		
Service time	ST	Years
Age	Age	Years
Sex	Sex	Code: 1 = males; 2 = females
Salaried/Hourly	S/H	Code: 0 = Salaried; 1 = Hourly
Job Status	JS	Code: 0 = Working; 1 = Separated
Plant Location	PL	Code: 0 = Ft. Edward; 1 = Hudson Falls
Disease Status	DS	Code: 0 = No disease; 1 = Intercurrent disease
Smoking Code	SC	Code: 0 = Nonsmokers; 1 = Smokers and ex-smokers
Alcohol Consumption	Alc	Code: 0 = None; 1-7 = occasional to heavy
Medications	Med	Code: -1 = Weak depressant; 0 = No effect; 1 = Weak inducer; 2 = Strong inducer

Table 3

PERSISTENT PCB CONGENERS IN CAPACITOR WORKERS EVALUATED AS PERCENTAGE COMPOSITION IN SERUM VS AROCLOR 1242 AND 1260 STANDARDS

Serum Percentage Compositions Are the Mean of 10 Workers; Parentheses Indicate Coeluting Isomers

No. Cl	IUPAC No.	Structure	Percentage Composition	
			Std.	Population
			Aroclor 1242	
3	28 (31)	2,4,4' (2,5,4')	8.1	21.5
4	70 (76)	2,4,5,4' (3,4,5,2')	1.6	33.0
5	99	2,4,5,2',4'	0.7	8.0
			Aroclor 1260	
5-6	118, 149 (106)	2,4,5,3',4'; 2,3,6,2',4',5' (2,3,4,5,3')	11.5	14.7
6	153 (105, 132)	2,4,5,2',4', 5' (2,3,4,3',4'; 2,3,4,2',3',6')	16.1	39.9
6	138 (160, 163, 164)	2,3,4,2',4',5' (2,3,5,6,3',4'; 2,3,4,5,6,3'; 2,3,6,3',4',5')	12.0	14.6
7	171 (156)	2,3,4,5,6,2',3',4' (2,3,4,5,3',4')	2.5	4.2
7	180	2,3,4,5,2',4',5'	12.4	6.4
8	194	2,3,4,5,2',3',4',5'	0.8	0.6

Table 4

GEOMETRIC MEAN GROSS SERUM PCB LEVELS IN VARIOUS STUDY POPULATIONS

Uncorrected Values as Reported by Laboratory
(Sum of Selected Peak Heights Method)

on	Year Measured	N	Aroclor 1242 (ppb)	Aroclor 1260 (ppb)	Service (years)
No Exposure (Nonplant Control)	1976	18	6.7	9.2	0
Laboratory Personnel (Nonplant)	1984	10	11.2	12.9	0
Employed since PCB Ban	1981	16	28.3	7.8	2
Employed, Not Exposed	1981	18	50.4	7.5	24
Exposed	1976	176	1469.0	-	14
	1979	171	273.0	35.1	17
	1983	146	120.6	31.5	22

Table 5

STATISTICALLY SIGNIFICANT ASSOCIATIONS OF GROSS SERUM AROCLOR 1242 WITH CANDIDATE CONFOUNDERS (TABLE 2) FOR COMPARABLE POPULATION IN 1976, 1979, AND 1983

Values Are Partial Correlations at End of Backward-Step Multiple Linear Regression; R^2 for Final Regression Equation Given Below

	1976	1979	1983
N	135	136	136
PCB Mean (ppb)	1518	289	124
Total Neutral Lipid	528	517	505
Exposure	0.73*	0.52*	0.48*
Total Neutral Lipid	0.27*	0.30*	0.25*
Fasting/Nonfasting	0.21	-	-
Fat	-	0.21*	0.19
Hourly/Salaried	-	0.18	0.25*
Sex	-	0.18	-
Service Time	-	0.21*	0.23*
Smoking	-	-0.24	-0.18
Albumin	-	-	-0.20*
R^2	58.8	52.5	47.1

*Significant associations with gross serum Aroclor 1260

Table 6

BIOCHEMICAL AND HEMATOLOGICAL VALUES REPORTED AS OUTSIDE AGE- AND SEX-ADJUSTED LABORATORY STANDARDS*

Clinical Variables	High			Low		
	Males	Females	Total	Males	Females	Total
Triglycerides	38	6	44	0	0	0
Total cholesterol	10	2	12	2	0	2
SGPT	17	1	18	0	0	0
SGOT	1	0	1	0	0	0
GGTP	11	5	16	1	0	1
Alk. Phosphatase	1	1	2	2	0	2
LDH	2	2	4	0	0	0
Blood glucose	10	5	15	0	0	0
Uric acid	10	2	12	2	0	2
Total bilirubin	0	0	0	0	0	0
Direct bilirubin	0	0	0	0	0	0
Total protein	0	0	0	1	1	2
Albumin	0	0	0	0	0	0
Globulin	0	0	0	0	0	0
A/G ratio	18	3	21	0	0	0
BUN	4	0	4	2	2	4
Creatinine	1	0	1	0	1	1
B/C ratio	6	6	11	1	0	1
Na	0	2	2	1	0	1
K	14	4	18	1	1	2
Cl	11	0	11	2	0	2
Ca	0	0	0	0	0	0
P	2	2	4	3	0	3
RBC	0	0	0	8	3	11
Hemoglobin	2	1	3	3	0	3
Hematocrit	4	2	6	6	0	6
MCV	4	3	7	0	0	0
MCH	10	3	13	1	0	1
MCHC	0	0	0	1	2	3
WBC	4	2	6	11	5	16
Differential						
PMNs	3	2	5	15	6	21
Lymphocytes	13	8	21	5	2	7
Monocytes	14	1	15	0	0	0
Eosinophils	11	3	14	0	0	0
Basophils	0	0	0	0	0	0
Urinalysis						
Albumin	1	0	1	0	0	0
Acetone	0	0	0	0	0	0

*Smith Kline Laboratories, Inc., King of Prussia, PA.

Note: All blood chemistries determined on serum; hematology measurements on EDTA venous blood.

Abbreviations:

- SGOT - serum glutamic-oxalacetic transaminase
- SGPT - serum glutamic-pyruvic transaminase
- GGTP - serum gamma glutamyl transpeptidase
- LDH - serum lactic dehydrogenase
- A/G ratio - albumin/globulin ratio
- BUN - blood urea nitrogen
- B/C ratio - blood urea nitrogen/creatinine ratio
- Na - serum sodium
- Cl - serum chloride
- Ca - serum calcium
- K - serum potassium
- P - serum phosphate
- RBC - red cell count
- HGB - hemoglobin
- HCT - hematocrit
- MCV - mean corpuscular red cell volume
- MCH - mean corpuscular red cell hemoglobin
- MCHC - mean corpuscular red cell hemoglobin concentration
- WBC - white blood cell count
- PMN - polymorphonuclear white cell count

Table 7

STATISTICALLY SIGNIFICANT PARTIAL CORRELATIONS OF BIOCHEMICAL AND HEMATOLOGICAL MEASURES (DEPENDENT VARIABLES) WITH VARIOUS MEASURES OF EXPOSUR DERIVED FROM SERUM PCB LEVELS, IN PRESENCE OF CONFOUNDERS

The Relation of the Percentage of Basophils and the Serum Lipid PCBs (Aroclor 1242) Was Removed When the Working/Separated Category Was Deleted as an Independent Variable (Shown by Parentheses); Partial R (0.95) = 0.165

Dependent Variable	N	Independent Variables: GS PCB	SL PCB	Age	Sex	S/H	PL	JS	DS	Fat	SC	Alc	Med	SPG
Aroclor 1242														
Log Triglycerides	146	0.21	-	-	-	-	0.16	-	0.33	0.27	-	-	-	-
Cholesterol	146	0.20	-	0.26	-	-	-	-	-	-	-	-	-	-
Basophils (%)	146	-	(-0.16)	-	-	-	-	(-0.16)	-	-	-	-	-	-
Aroclor 1260														
Log Triglycerides	146	0.36	-	-	-	-	-	-	0.33	0.29	-	-	-	-
Cholesterol	146	0.27	-	0.34	-	-	-	-	-	-	-	-	-	-
Log SUM	146	0.31	-	0.30	-0.20	-	-	-	-	-	-0.17	-	-	0.31
Log S/C Ratio	146	0.26	-	0.21	0.25	-	-	-	-	-	-	-	0.20	0.28

Abbreviations:

S/H - salaried or hourly worker
PL - plant location as of 1976
JS - working or separated
DS - absence or presence of intercurrent disease
SC - smokers or nonsmokers
Alc - alcohol consumption code
Med - use of mixed function oxidase drugs
SPG - specific gravity of urine

Table 8

SIGNIFICANT PARTIAL CORRELATIONS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE AMONG 19 INDEPENDENT VARIABLES

	Fat	Age	HMed	Med	Sex	HHY	SC
Systolic blood pressure	0.28	0.22	0.20	0.17	-	-	-
Diastolic blood pressure	0.31	-	0.17	-	-0.19	0.19	-0.17

Abbreviations:

HMed - diuretics, beta-blockers
Med - MFO inducers (diazepam)
HHY - reported history of hypertension
SC - smoking code

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FOLLOW-UP STUDY OF CAPACITOR WORKERS EXPOSED TO POLYCHLORINATED BIPHENYLS (PCBs)

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