Polychlorinated Biphenyl Exposure and Human Disease

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Polychlorinated biphenyls (PCBs) continue to be of great environmental and occupational health interest. This review summarizes the major clinical findings reported in individuals incurring the greatest PCB exposure—those persons working in the manufacture or repair of electrical capacitors or transformers. The potential target organs addressed in the studies reviewed include the liver, lungs, skin, cardiovascular system, nervous system, certain endocrine systems, the blood/immune system, and the gastrointestinal and urinary tracts. After careful analysis, the weight of evidence suggests the only adverse health effects attributable to high, occupational PCB exposures are dermal. This review confirms and extends the observations of others, ie, that the collective occupational experience with PCB fluids provides no evidence for adverse PCB effects on any other organ systems.

Despite their discontinued manufacture, the persistence of polychlorinated biphenyls (PCBs) in the environment has caused them to remain a significant human health concern. Literature available to define the human-toxicology of PCBs includes clinical and scientific reports spanning over 50 years. This literature, though extensive, is somewhat fragmented. While there are many studies of potential PCB effects within discrete study populations, little is available in the way of comprehensive reviews of the human health effects of PCBs.

Clinical studies of potential PCB health effects have been conducted in basically three types of study populations. The first represents a rather special population—individuals poisoned with rice oil contaminated with PCBs. Two widespread outbreaks of contaminated rice oil poisoning have occurred, one in Japan in 1968 and the other in Taiwan in 1979. The symptoms of these rice oil poisonings, termed "Yusho" in Japan and "Yu-Cheng" in Taiwan, were similar and originally attributed to PCBs present in the oil. However, further examination of the poisoning incidents found several lines of evidence indicating that the symptoms were most probably caused by the presence of the more potently toxic polychlorinated dibenzofurans (PCDFs). This evidence includes the observation that PCB levels in Yusho and Yu-Cheng victims with severe manifestations of disease were no greater than those of healthy PCB-exposed workers, while their PCDF levels were much higher.[1,2] Furthermore, studies in monkeys were able to duplicate Yusho-like symptoms with a mixture of PCBs and PCDFs resembling the toxic rice oil, or with the PCDF component

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alone, but not with a mixture containing the PCBs without PCDF.[3] There is now general agreement among investigators most familiar with the rice oil poisoning incidents that they represent primarily PCDF intoxications[2,4–12] and, therefore, have little relevance in defining the toxicity of PCBs in humans. They did, however, provide a stimulus for subsequent, more instructive studies of potential PCB-related health effects.

A second type of study population consists of individuals exposed to PCBs in the environment. Typically the source of environmental exposure in these studies was PCBs found in nearby soils or in the diet (usually in fish). While these studies conceivably have value in ascertaining the potential health effects of PCBs, they are often severely limited by low or equivocal PCB exposures and/or the presence of concurrent exposures to other chemicals that confound the interpretation of results.

The third type of study population is workers exposed to PCBs in an occupational setting. Exposures to PCBs among workers in some occupations (eg, capacitor or transformer manufacture) were very high, and some study populations contain workers with job-related exposures of 20 years of more. Both the magnitude and duration of exposures in PCB worker studies provide the best opportunity to clearly observe which kinds of health effects might reasonably be attributable to PCBs. As such, studies of PCB-exposed worker populations may be considered to be inherently the most valuable.

The purpose of this review is to critically summarize available studies relevant to potential human health effects of PCBs. Clinical studies dealing with both environmental and occupational PCB exposure have been considered, although, for the reasons listed above, the environmental studies have been given less weight in the final analyses. Where appropriate, inferences from mortality studies have also been included in this analysis. Reports concerning Yusho and Yu-Cheng have been omitted since, as indicated above, it is doubtful that they can provide information relevant specifically to PCB toxicity. Potential health effects addressed in this review include effects on the skin, liver, lungs, serum lipids or lipoproteins, the cardiovascular system, the nervous system, the blood and immune system, the gastrointestinal and urinary tracts, and some endocrine functions. Information concerning the potential human carcinogenicity or reproductive/developmental effects of PCBs will be the subjects of separate reviews.

Descriptions of the Occupational Cohorts

The occupational cohort studies considered in this review are briefly described in tabular form (Tables 1 and 2). The largest cohorts of persons known to have experienced appreciable occupational PCB exposure in the workplace involved employees of companies manufacturing electrical equipment, particularly those persons who filled large capacitors and transformers with PCB-containing fluids. Four large capacitor manufacturing plants located in the midwestern and northeastern United States have been studied in great detail (Table 1). These plants employed thousands of people during periods of moderate to heavy PCB usage, and several studies have been published that contain extensive clinical data derived from cross-sectional surveys of workers from these plants. To a lesser extent, the health of employees from capacitor manufacturing plants from other countries have also been studied. These studies, although helpful, tend to be of lesser significance, either because of the small number of workers evaluated[13–17] or because the magnitude of PCB exposure to the cohort selected was probably not as great as that experienced by US capacitor manufacture workers.[18–20] Clinical observations have also been obtained from three cohorts of transformer repair workers, two cohorts of PCB manufacture workers, one cohort of silk thread manufacturers, one cohort of marine paint workers, and one group of employees exposed to heat transfer fluids (Table 2). As with the foreign capacitor worker studies, these cohorts were, in general, considerably smaller than the US capacitor worker cohorts.

Table 3 characterizes individual study qualities and deficiencies for the broad clinical surveys of PCB-exposed workers. All of these surveys performed health and exposure history analyses and sought statistical correlations between the clinical parameters and PCB exposure (as determined primarily by serum PCB levels). A description of exposure was provided in most studies in that limited workplace PCB measurements, hygiene descriptions, or exposure duration data were at least summarily noted for the study population. The scope of the clinical surveys was often good, providing information on multiple organs and systems, and a number of the surveys analyzed clinical parameters pertaining to at least five of the nine general areas reviewed. However, few studies included values from a matched control group in their analysis of the data.

An important consideration in the evaluation of occupational cohort studies is the confounder of multiple chemical exposure. All of the studies reviewed involved exposure to other chemicals, principally those organic solvents, additives, or contaminants associated with industrial uses of PCB fluids or commercial mixtures containing PCBs as a major component. Since the potently chloracnegenic PCDFs were generally present at part per million levels in commercial PCB fluids, low-grade PCDF exposure is common to all PCB-exposed cohorts. In addition, experience has shown that, with high temperatures and in the presence of oxygen, additional PCDFs may be formed from PCBs. As a consequence, a few of the studies[14–16] are confounded by the fact that explosions of capacitors during stress testing may have created unusually high exposure to PCDFs for some of the workers in their study. Similar reservations are also held for the early dermatological survey of Meigs et al[21] because this study involved worker exposure to vapors emanating from an open-air sump system where PCBs

TABLE 1
PCB Capacitor Plant Cohort Study Information

Cohort Size and Location	PCB Usage Interval	Study Authors and Year	Study Type	Number of Study Subjects
Indiana				
3,588 total workers	1959–1977	Smith et al, 1982[38]	Broad clinical survey	228
		Sinks et al, 1992[42]	Mortality analysis (192 deaths)	3,588
Massachusetts				
1,559 workers in PCB-exposure jobs	1938–1977	Lawton et al, 1985[23]	Broad clinical survey	194
		Brown and Jones, 1981[26]	Mortality analysis (90 deaths)	1,599
		Brown, 1987[40]	Mortality analysis (179 deaths)	1,607
500 current workers	1941–1977	Acquavella et al, 1986[41]	Broad clinical survey	205
New York				
6,303 total workers at the two plant locations; 2,588 in PCB-exposure jobs	Plant 1: 1951–1977	Alvares et al, 1977[27]	Liver function survey	5
	Plant 2: 1946–1977	Fischbein et al, 1979[24]	Broad clinical survey	326
		Warshaw et al, 1979[28]	Lung function survey	326
		Brown and Jones, 1981[26]	Mortality analysis (73 deaths)	968
		Fischbein et al, 1982,[27a] 1985[29a]	Dermal/ocular effect survey	181–289
		Fischbein, 1985[40]	Liver function survey	261
		Lawton et al, 1986[53]	Lung function survey	194
		Nicholson et al, 1987[60]	Mortality analysis (188 deaths)	788
		Brown, 1987[40]	Mortality analysis (116 deaths)	981
		Taylor, 1988[61]	Mortality analysis (510 deaths)	6,303
Australia				
34 PCB-exposed workers	1951–1974	Ouw et al, 1976[13]	Dermal effects/liver function	34
Italy				
1,310–2,100 total workers	1946–1980	Maroni et al, 1981b[15]	Dermal effects/liver function	80
		Maroni et al, 1984[16]	Enzyme induction/porphyria	51
		Bertazzi et al, 1987[20]	Mortality analysis (64 deaths)	2,100
Japan				
155 possibly exposed workers	1948–1972	Hara, 1985[18]	Limited clinical survey	155
Sweden				
145 exposed workers	1965–1978	Gustavsson et al, 1986[17]	Mortality analysis (21 deaths)	142

were used as heat exchanger fluids. Last, the study of Jones and Alden[22] is confounded by the fact that an impure batch of benzene was used in the synthesis of the PCBs involved in that particular incident and the dermal lesions were ultimately attributed by the authors of this study to chlorinated contaminants rather than the PCBs.

In addition to PCDFs, other chemical exposures were associated with the use of PCB fluids and their presence should be considered a potential confounder of the results reported in the studies reviewed here. PCBs were commonly mixed with chlorinated benzenes (generally 30%–40% by volume) for use in large-capacity transformers and capacitors. Upon combustion, these chlorinated benzenes may form both PCDFs and polychlorinated dibenzo-p-dioxins. Investigators of the major PCB capacitor worker cohorts[23,24] noted the usage of chlorinated benzenes in the PCB fluids for capacitors, but other investigators of capacitor workers and transformer repair workers did not specify whether chlorinated benzenes were utilized. Unfortunately, in no case was exposure to chlorinated benzenes measured and compared to that of the PCBs.

Other likely but largely unspecified exposures to chemicals associated with PCB fluids include stabilizers like the alkylbenzenes or certain epoxides. Although these stabilizers were no doubt only a small component of the PCB fluids to which they were added, Lawrence[25] has pointed out that their much higher vapor pressures may have resulted in a substantial workplace exposure to these compounds. Another potentially confounding factor common to these studies was exposure to chlorinated organic solvents like trichloroethylene and/or 1,1,1-trichloroethane that were used to clean up PCB spills and to degrease equipment and final products. While some studies did address the potential confounder of exposure to other chemicals,[26–28] there is little indication that other investigators considered the potential importance of the cohort's exposures to solvents or other workplace chemicals.

In addition to contaminants and stabilizers, PCB substitutes were in-

TABLE 2
Cohort Information for Transformer Repairmen and Other PCB-Exposed Workers Studied

Cohort Size and Location	PCB Usage Period	Study Authors and Year	Study Type	Number of Study Subjects
Alabama				
PCB manufacturing; 24 production workers	Not specified	Jones and Alden, 1936[22]	Dermal survey	24
Delaware				
Locomotive repair; 120 total employees	1939–1979?	Chase et al, 1982[27]	Broad clinical survey	101
Illinois				
PCB manufacture; 89 exposed workers	Not specified	Zack and Musch, 1979[54]	Mortality survey (30 deaths)	88
Midwestern United States				
Transformer repair; 93 exposed workers	Not specified	Smith et al, 1982[38]	Broad clinical survey	93
Washington, DC				
Switch gear repair; 120 total employees	Not specified	Emmett, 1985[39]	Liver function survey	55
		Emmett et al, 1988a, b[29,30]	Broad clinical survey	55
Other, United States				
PCBs used in heat exchange; 14 employees	Not specified	Meigs et al, 1954[21]	Dermal survey	14
Japan				
Silk thread or marine paint factory workers; 112 workers	1966–1972	Takamatsu et al, 1985[19]	Limited clinical survey	112

TABLE 3
Data-Base Characteristics for the Broad Clinical Surveys of PCB-Exposed Workers

Study Author	Fischbein et al[24]	Lawton et al[23]	Smith et al[38]	Chase et al[27]	Emmett et al[29,39]	Acquavella et al[41]
Study features and confounders						
Study group size (exposed)	326	194	321	101	55	205
Test values reported	No	Yes	No	Yes	Yes	No
% abnormal reported	Yes	Yes	No	No	No	No
Correlative studies	Yes	Yes	Yes	Yes	Yes	Yes
Matched control group	No	No	No	No	Yes	No
Health history	Yes	Yes	Yes	Yes	Yes	Yes
Non-PCB exposures reported	Yes	Yes	Yes	Yes	Yes	Yes
Organs/systems analyzed						
Skin	Yes	No	Yes	Yes	Yes	Yes
Liver	Yes	Yes	Yes	Yes	Yes	Yes
Hematopoietic	Yes	Yes	Yes	Yes	Yes	Yes
Pulmonary	Yes	No	No	No	Yes	No
Neurological symptoms	Yes	No	No	No	Yes	No
Gastrointestinal symptoms	Yes	No	Yes	No	Yes	No
Serum lipid levels	Yes	Yes	Yes	Yes	Yes	Yes
Kidney	Yes	Yes	Yes	Yes	Yes	No
Cardiovascular	No	Yes	Yes	No	Yes	No
Endocrine	Yes	No	Yes	No	Yes	No
PCB exposure characterization						
PCB air or surface levels	Yes	Yes	Yes	Yes	Yes	Yes
Hygiene descriptions	Yes	Yes	Yes	Yes	Yes	Yes
Serum PCB measurements	Yes	Yes	Yes	Yes	Yes	Yes
Adipose PCB measurements	No	No	No	Yes	Yes	No
Exposure duration reported	Yes	Yes	No	Yes	Yes	No
Clinical evidence of exposure (chloracne)	Yes	No	No	Yes	No	No

corporated into the processes of all the major cohorts during 1977. The substitutes used included β-chloranthroquinone, dioctylphthalates, dibutylsebacate, and mineral oil (New York, Massachusetts, northeastern US), and isopropylbiphenyl (Indiana). As many of the cohorts were examined (or reexamined) some time after 1977, the more recent daily exposure to these substitutes confounds any analysis of these studies.

It is unfortunate that only limited discussions were provided by most authors concerning the alternate chemical exposures that were present in these studies. It is apparently assumed by most investigators that only PCB exposures were to be associated with the clinical findings they reported. Since the actual impact of the confounding chemical exposure is unknown, it is particularly important when reviewing the PCB literature that the observations of any study be confirmed by other investigations.

Categorical Review of Clinical Studies

Effects on the Skin

Various skin conditions have been reported in humans occupationally exposed to PCBs. Dermal conditions observed in workers in these studies include dermatitis,[15] temporary inflammation or edema of the skin and eyes,[27a] a thickening of the skin and fingernails,[24] and chloracne.[15,21,22,29a] Complaints such as rashes or skin irritation have been typically reported in the absence of serious skin conditions or documented high exposure to PCBs. These minor dermatological complaints may be more related to low-grade exposure to epoxide additives in the PCB fluids or caused by the workers' concomitant exposure to chlorinated benzenes, organic solvents, or harsh detergents that were also present when viscous fluids like PCBs were used industrially.[25,30] Other dermal effects such as thickening of the skin, temporary inflammation or edema of the skin and eyes, and chloracne appear to be related to the incidence and magnitude of the individual's dermal contact with PCB fluids or result from high exposure to heated PCB vapors, suggesting PCBs (or PCDFs) as the causative agent.

A dermal effect associated with PCBs of particular interest is chloracne. Chloracne is a dermatologic condition characterized by blackheads, pustules and/or cysts, and generally appears on the malar regions of the face, the scalp, and the back of the neck. When induced by halogenated aromatic compounds, chloracne may sometimes be quite persistent. Only two early studies reported observing a relatively high incidence of chloracne associated with PCBs. In one of these studies, workers manufacturing PCB fluids were believed to have been exposed to chlorinated byproducts generated by the use of impure benzene in the synthesis of PCBs.[22] The second study consisted of workers exposed to leaking heat exchanger fluids,[21] and, therefore, may represent a situation more like the PCDF exposures associated with Yusho and Yu-Cheng. Still, a low incidence of acne-like lesions has been reported in a number of the more recent studies of occupationally exposed PCB workers, and this condition would appear to be a potential effect of high, chronic exposure to PCBs. The chloracne observed in the occupational setting was generally associated with high body burdens of PCBs (eg, hundreds to sometimes thousands of parts per billion of PCBs in serum), though individuals with excessive PCB body burdens (>1,000 ppb PCBs in serum) often do not develop chloracne.[13,15] There are at least three possible explanations for the inconsistent appearance of chloracne in individuals with high body burdens. One potential explanation is a difference in susceptibility among workers to PCB-induced chloracne. A second explanation is a misclassification or misdiagnosis of the acne-like lesions due to the absence of histological confirmation. A third explanation for the inconsistent results is that the chloracne, and perhaps also other oculodermal effects, are caused by a contaminant (ie, PCDFs) rather than PCBs.[27a,29a] PCDFs were not routinely measured in either the fluids or the individuals of any of these studies, and, based on the findings of Yusho and Yu-Cheng incidents, PCDFs are relatively potent chloracnegens.

In contrast to the above reports, studies of environmental exposure to PCBs, primarily through contaminated fish consumption,[31] contaminated sludge use,[32] or residence near a PCB waste site[33] have not demonstrated the occurrence of chloracne or any other significant dermal effect or chronic skin disease. Studies examining low-level or short-term exposure to PCBs after a spill[34] or through sewage treatment operations[35] also failed to demonstrate significant acute or chronic dermal conditions attributable to PCBs.

Hepatic Effects

Studies in animals indicate that PCBs induce hepatic drug metabolism and at higher dosages may cause liver toxicity.[36] Evidence for both of these effects has been sought in clinical studies of PCB exposure. With respect to hepatic enzyme induction, three approaches have been used for its detection. One approach has been to measure the rate of elimination of a test dose of antipyrine, a known substrate for hepatic enzymes. Alvares et al[27] found the average half-life of antipyrine in five capacitor workers exposed to PCBs to be significantly less than the average half-life in five control subjects (10.8 hours versus 15.6 hours), suggesting an hepatic induction effect associated with PCB exposure. In contrast, a much larger series evaluated by Emmett et al,[29,30] found the mean half-life of antipyrine in forty-seven PCB-exposed workers to be higher than, but not significantly different from, the average half-life in forty-four controls (12.4 hours versus 10.7 hours). The reason for this difference in observations is unclear, but could conceivably be due to differences in extent of exposure for the two study populations.

A second approach has been through measurement of serum γ-glutamyl transpeptidase (GGT) activity, a parameter whose increase might, among other possibilities, suggest the occurrence of hepatic enzyme induction.[37] None of the many studies that measured serum GGT activities found average values in PCB-exposed workers that were abnormal or significantly increased compared to control subjects. The evidence for serum GGT as an indicator of PCB exposure is equivocal. A number of investigators reported a correlation between serum PCB levels and serum GGT activities,[23,29,32,37–40] while other investigators found no correlation between serum PCBs and serum GGT,[24,41] or that such correlations are lost when

the results are adjusted for alcohol consumption in the subjects.[28,36,37]

The third approach has been to measure urinary D-glucaric acid levels,[16] a test that purportedly reflects changes in hepatic microsomal glucuronidation. While PCB-exposed workers had a significantly increased D-glucaric acid excretion in this study, no correlation between this measurement and PCB blood levels was found, making it difficult to attribute these differences to PCBs.

Currently, there is no clinical evidence for toxic effects on the liver due to PCB exposure, even among electrical workers with extensive PCB body burdens. In general, the results of a number of studies conducted from 1976 through 1988 have revealed that occupationally exposed groups were within the expected normal limits, or that the number of persons falling outside the normal range was not significantly greater than that anticipated.[13,24,29,37-41] For example, studies by Ouw et al[13] and Emmett[29,39] either reported mean values for liver function tests that were shown to fall within the normal range for each test, or the mean values were not significantly different from that of the control population. The study of Fischbein et al,[24] one the largest study populations examined to date, is also illustrative as they reported the frequency of normal liver function test values for their PCB-exposed population to be 97.8% for serum aspartate aminotransferase (AST) activity, 92.8% for serum alanine aminotransferase (ALT) activity, 97.5% for serum lactate dehydrogenase (LHD) activity, 98.1% for serum GGT activity, 98.8% for serum alkaline phosphatase activity, and 94.7% for serum bilirubin levels. These high percentages are remarkably consistent with the fact that only about 95% of any normal population is expected to have values that fall within a "normal" range defined as two standard deviations about the mean value. Given that 66% of the population examined by Fischbein et al[24] was 40 years of age or older, and that 70% of this population had been exposed for more than 10 years, this study, perhaps more than any other, indicates that the occupational exposures to PCBs did not produce liver toxicity.

While correlations between serum PCB levels and the numerical value for one or more different liver function tests have been reported, there is no liver function test for which such correlations have been consistently found, and in each case the correlation was observed in a study where no excess number of abnormal test values was reported. For example, a correlation between serum PCB levels and serum AST activity (or its log-transformed value) has been reported in three studies,[24,37,38] but was not found in four similar studies.[23,29,39,40] The intermittent finding of these correlations, correlations that are being reported in populations with normal liver function tests, has no apparent toxicological or physiological meaning and may instead merely arise from the large number of statistical comparisons being performed in these studies.

An unusual observation of increased incidence of hepatomegaly among PCB-exposed workers was reported in one study.[15] A total of 16 workers from a cohort of 80 were regarded as having "hepatic involvement," either in the form of hepatomegaly or one or more elevated liver enzyme tests. Among workers in plant B, where exposure included PCBs dispersed by explosions during stress testing of capacitors, the incidence of hepatomegaly was especially high—more than 50% (7/13). While a relationship between serum PCB concentrations and the appearance of hepatomegaly was asserted in this study, there was no apparent relationship between serum PCB levels and severity of hepatomegaly. More importantly, the virtual absence of hepatomegaly among the numerous other clinical studies of PCB-exposed workers[13,23,24,29,30,32,37-41] makes it difficult to attribute this observation simply to PCB exposure. It is unlikely that the discrepancy between this study and others is a matter of degree of PCB exposure, since at least two other studies[23,24] have conducted physical examinations on study populations with serum PCB levels as high or higher (up to 3,850 ppb) than those in the Maroni et al[14-16] study group with no reported hepatomegaly. It is possible that the nature of the exposure of this Italian population of PCB workers was unique, perhaps including an unusually high exposure to PCDFs formed during capacitor explosions. With respect to liver function tests, abnormal results occurred randomly and were generally too small to be considered clinically significant. In no case were any of the small elevations in liver enzymes confirmed by retesting. Among the 67 workers in plant A, where exposures were not confounded by potential PCDF formation from capacitor explosions, the number of minimally elevated serum ALT, serum AST, and serum GGT values was that expected for a population of normal, healthy individuals (ie, <5%). Furthermore, no relationship was apparent between the occasional abnormal values and PCB exposure (Table 4); for individual liver tests, there were no significant differences in serum PCB levels between those with normal and abnormal test values.

In conclusion, while the results of one study using antipyrine clearance have suggested hepatic enzyme induction in workers exposed occupationally to PCBs, other studies using this and other approaches have not found induction attributable to PCB exposure. The possibility of toxic effects in the liver associated with PCB exposure has been examined in detail in several studies. Clinical measurements reflective of liver toxicity from the various studies have been consistently negative.

In spite of evidence for hepatotoxic potential of PCBs in animal studies, the absence of adverse liver effects in PCB-exposed workers should not necessarily be considered a surprising finding. The early concern for workplace exposures was the prevention of liver and dermal toxicity,[42,43] and this is clearly reflected in the initial threshold limit values of 1.0 mg/m^3 (42% chlorine mixtures) and 0.5 mg/m^3 (54% chlorine mixtures) that were first established by the American Conference of Governmental and Industrial Hygienists in 1959. These guidelines were lower than those of 2.0 mg/m^3 (42% chlorine mixtures) and 1.0

TABLE 4
Comparison of Mean Serum PCB Levels between Individuals with and without Abnormal Liver Function Indicators in the Cohort of Maroni et al (1981b)[15]

Test (Group Results)	Number of Workers	Mean PCB Blood Level ± SEM (ppb)	t-test (P Value)*
Serum alanine aminotransferase			
Normal values	10	627 ± 123	
Elevated values	6	352 ± 76	NS (0.13)
Serum aspartate aminotransferase			
Normal values	13	542 ± 104	
Elevated values	3	411 ± 142	NS (0.58)
Serum ornithine-carbamoyl transferase			
Normal values	10	440 ± 110	
Elevated values	6	663 ± 136	NS (0.23)
Serum γ-glutamyl transpeptidase			
Normal values	8	648 ± 157	
Elevated values	8	400 ± 60	NS (0.16)

* Data derived from Maroni et al (1984)[15] was subjected to the Student's *t*-test for unpaired values. NS (no significant difference at $P < .05$).

mg/m³ (54% chlorine mixtures) proposed earlier by Treon et al[44] as apparently protective of liver toxicity based on animal studies performed by these authors. The initial threshold limit values were also well below the 10.5 mg/m³ measured-air PCB concentrations in Massachusetts plants that Elkins[41] reported as having produced no evidence of toxicity other than irritation. More recently, Lawton et al[23] have pointed out that the doses and tissue levels of PCBs causing liver damage in rodents are some three to four orders of magnitude greater than those experienced occupationally.

Effects on Serum Lipid or Lipoprotein Levels

Many of the clinical studies of both occupational and environmental exposure to PCBs have included measurements of serum lipids, but no adverse effect of PCB exposure on serum lipid levels has ever been demonstrated. Clear evidence of an absence of significant clinical abnormalities in lipid metabolism has been provided in five studies of PCB-exposed workers. Baker et al[32] studied 148 persons exposed to PCBs both occupationally and environmentally and found no excess clinical abnormalities in serum triglycerides, total cholesterol, or high-density lipoprotein (HDL)-cholesterol among exposed persons. Likewise, Smith et al[38] studied 274 capacitor/transformer workers who sustained high-level PCB exposures and found no excess clinical abnormalities in serum triglycerides, total cholesterol, or HDL-cholesterol among exposed persons. After comparing the mean values between PCB-exposed and matched control groups, no significant differences were found by Chase et al[37] in the mean serum triglycerides, total lipids, total cholesterol, or HDL-cholesterol of 120 locomotive repair workers, or by Emmett[29,39] in the mean serum triglycerides, total lipid, total cholesterol, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, or very low-density lipoprotein (VLDL)-cholesterol of 55 transformer maintenance/repair workers.

As with the serum liver enzyme correlations, a statistical correlation between serum PCB levels and the levels of some component of serum lipids have been reported in a number of studies. The two most common correlations were between serum PCBs and serum triglyceride levels,[23,29,37,38,45] and serum cholesterol levels.[23,29,45] While some have postulated that these correlations suggest a possible effect of PCBs on lipid metabolism, a review of all available evidence finds several facts that argue strongly against this supposition. First, no consistent correlation has been found in the clinical studies of either occupational or environmental exposures. Instead, the type of correlation varies among the studies; some studies reported a correlation for PCBs with triglyceride levels and not cholesterol levels and others reported correlations for cholesterol levels and not triglyceride levels. Similar conflicting correlations are also found among the clinical studies of environmental exposures to PCB.[31-35,46] Second, of five studies examining PCBs and serum lipids, none noted a significant excess of abnormal lipid values or a significant difference between control and PCB-exposed groups in total lipid, serum triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, or VLDL-cholesterol levels.[29,32,37-39] Thus, as with the liver enzyme correlations, the correlations between serum PCB levels and serum lipid levels are found among persons with normal rather than elevated serum lipid values, and, consequently, these correlations have no toxicological significance. Third, conflicting correlations have been observed both among environmentally exposed persons (low exposure) and occupational (high exposure) studies, suggesting this phenomenon is unrelated to dose. As demonstrated by two recent studies,[23,39] these correlations can be explained by the natural partitioning of PCBs to serum lipids.

Emmett[39] examined 55 transformer maintenance workers and initially found statistical correlations between log serum PCBs and log triglyceride, total cholesterol, and log VLDL concentrations. These observations of Emmett were consistent with the various correlations between serum PCBs and lipid levels that have been reported by others. However, Emmett performed additional analyses to demonstrate that these correlations were of no medical consequence.

First, he demonstrated that the correlations between serum lipid measurements and serum PCB levels could be found even though the mean serum lipid levels of the PCB-exposed group were not significantly different from those of the control group. That is, these correlations existed even though the serum lipid levels of the PCB-exposed population had not been elevated by exposure. Second, no correlation was found between adipose PCB levels, a better indicator of PCB body burden than serum measurements, and any serum lipid component. If tissue PCB levels do not correlate with serum lipid levels, then one cannot propose some target organ toxicity as the cause of the elevation in serum lipid levels. Confirming this conclusion, Emmett found that all serum PCB and serum lipid correlations became nonsignificant when he controlled for potentially confounding variables such as alcohol intake, liver disease, history of diabetes, heart disease, etc. Based on these observations, Emmett proposed the serum PCB-lipid correlations could be explained chemically rather than toxicologically. Due to their lipophilic nature, the movement of PCBs into blood will be driven by the partitioning of PCBs between adipose tissue and lipids in the blood, principally triglycerides and cholesterol. Therefore, the solubility of PCBs in the blood is a function of blood lipid content, and blood with higher triglycerides or cholesterol will contain more PCBs. This finding indicates that the observed correlations exist because serum lipid levels are affecting serum PCB levels rather than PCB exposure affecting serum lipid levels.

Lawton et al[23] provided an extensive analysis of clinical chemistry and hematological data from a group of 194 capacitor workers examined on two occasions. When correlation coefficients were calculated for log serum PCB levels and serum lipids, the correlations were significant between PCBs and log serum triglycerides and cholesterol, similar to reports by others. However, when the correlation coefficients were calculated using the log PCB concentration in serum lipids, the associations disappeared. Thus, this finding provides further confirmation that the associations between gross serum PCB levels and serum lipid levels can be explained simply by the partitioning behavior of PCBs.

The findings of these two studies[23,39] provide insight concerning the numerous inconsistent correlations between serum lipid levels and serum PCB concentrations reported by others. First, the inconsistency in reporting may be explained, at least in part, by the failure of studies reporting correlations to control for those variables of the individual (eg, age, alcohol consumption, medical history) that may affect serum lipid levels. Second, these correlations are of no medical or toxicological significance because they exist in groups of individuals with normal lipid levels. Third, since there are no correlations between serum lipid levels and adipose tissue PCB levels, and as tissue levels are the better measure of body burdens and total dose received, there really is no correlation between PCB dose and serum lipid levels. Fourth, both studies demonstrate that associations with gross serum PCB levels and serum lipid levels are easily explained by the partitioning behavior of PCBs.

Effects on the Cardiovascular System

Kreiss et al[31] reported a significant correlation between log serum PCB levels and increases in diastolic blood pressure in a cohort of 458 Alabama residents exposed to higher-than-normal levels of PCBs and DDT via the ingestion of local contaminated fish. The magnitude of the changes in blood pressure was not reported, but the authors stated the rates of borderline and definite hypertension were 30% higher than expected. Definitive conclusions from this study were prevented by the lack of a matched control group, and later recognition that the co-linearity of PCB and DDT levels in these individuals precluded assignment of any observation to either chemical alone.[47] Several studies of environmentally exposed cohorts have subsequently attempted to reproduce this observation of elevated blood pressure, but have failed to do so. Stehr-Green et al[33] found no excess of heart disease or hypertension in individuals living near PCB-containing hazardous waste sites and, after controlling for confounding variables, found no correlation between log serum PCB levels and log diastolic blood pressure. A relationship between PCBs and hypertension was also not observed in another, much larger study of environmental exposure to PCBs via consumption of contaminated fish.[48] Mean heart rate and blood pressure were also normal in a cohort of sewage treatment workers potentially exposed to PCBs.[35] Therefore, the initial evidence suggesting that PCB exposure may affect blood pressure is not convincing and has not been supported by subsequent studies of environmentally exposed populations.

If environmental exposure to PCBs does lead to hypertension or any other form of cardiovascular disease, an increase in cardiovascular disease and mortality should be easily observed in studies of individuals occupationally exposed to PCBs. Only two investigations have specifically reported findings related to cardiovascular status, but several studies have addressed potential cardiovascular effects through blood pressure measurement, complete physical examinations, chest radiographs, and/or medical histories. None reported an excess occurrence of high blood pressure or any other cardiovascular abnormality.[15,19,24,28,29,30,32,37] Of the two studies reporting specific findings, Smith et al[38] found that no correlation existed between log serum PCBs and diastolic blood pressure when adjusted for worker age and sex, and Lawton et al[23] reported "no evidence for health impairments related to PCBs" after analyzing the incidence of hypertension and results of electrocardiograms and chest radiographs for each worker in their cohort. Lawton et al[23] further noted that, "Despite the prevalence of cardiovascular risk factors (obesity, elevated cholesterol levels, smoking, etc) the mortality experience has been normal." Confirming this lack of effect of PCBs on the cardiovascular

system, none of the major mortality studies completed to date have found any association between PCBs and cardiovascular disease including hypertension.[26,49-52] In fact, a less-than-expected mortality from heart diseases has been observed in two of these studies.[51,52]

Effects on the Lungs

The relationship between pulmonary function and PCB exposure has only been evaluated in some detail in three studies of two different populations occupationally exposed to PCBs. Pulmonary function tests and chest radiographs have been used, along with questionnaires dealing with respiratory-related symptoms. In an initial examination of pulmonary function in US (New York) capacitor workers, reported respiratory symptoms included upper respiratory tract irritation (50% of workers), wheezing (3%), tightness in the chest (10%), and "work-related" cough (14%).[24,28] In the absence of a comparison population matched for age and smoking status, it is unclear which of these might be in excess. Spirometric tests found 14% of examined workers with diminished vital capacity and 11% with restrictive impairment. Chest radiographs in all but one case of restrictive impairment were normal, an unusual finding if there was in fact pulmonary impairment due to occupational exposure.

In a follow-up study of the same population, no spirometric abnormalities were found.[53] In view of the absence of evidence of pulmonary impairment on follow-up, and the failure of chest radiographs to confirm restrictive impairment in the first examination, the authors concluded that the original restrictive impairment finding was "*artifactual due to test operator inexperience and inadequate expiratory efforts.*" No correlation of spirometric variables with past exposure or serum PCB levels was found in the follow-up study, and, from this cohort, no evidence of an association between PCBs and respiratory disease has emerged.

Emmett et al[29,30] reported that 40% of exposed transformer repair workers complained of wheezing compared to a 20% incidence among controls. However, the wheezing was not correlated with the extent of PCB exposure (in terms of exposure history, log serum PCB levels, or log adipose PCB levels) or with objective measurements of respiratory function. Among the respiratory parameters measured, only the forced expiratory volume in 1 second was significantly lower in the PCB-exposed workers compared with controls; but this difference did not correlate with PCB body levels and was eliminated when the results were corrected for smoking status. Therefore, this study of transformer repair workers was similar to those of capacitor workers in that it provided no indication that chronic, occupational PCB exposures adversely affect pulmonary function.

Clinical investigations of respiratory function or complaints related to environmental PCB exposure are consistent with the negative evidence provided by studies of occupationally exposed persons.[33-35] Furthermore, the available mortality analyses of PCB-exposed workers have not revealed a significant excess of deaths from nonmalignant respiratory diseases.[17,50,51,52,54] Therefore, with the possible exception of the irritation that might be produced at some levels with any halogenated compound, the collective evidence demonstrates that chronic PCB exposure is not associated with pulmonary dysfunction or respiratory diseases.

Effects on the Blood and Immune Systems

Clinical studies examining blood cell counts and red blood cell parameters in PCB-exposed individuals have not reported an increased prevalence of any particular abnormality or generalized syndrome which suggests hematotoxicity. The extent of analyses in these studies varied considerably, from simple determinations of hemoglobin content and hematocrit to complex statistical analyses of various hematologic parameters versus blood concentrations of higher chlorinated and lower chlorinated PCB homologs. In perhaps the most thorough study of its kind, Lawton et al[23] compared serum PCB levels in capacitor workers with a variety of hematological parameters. Data were available from examinations of the workers conducted in 1976 (n = 194) and 1979 (n = 174). No associations were found between PCB blood levels and parameters related to red blood cells. Elevated lymphocyte counts were noted in the first examination (1976), but of these only an elevation in monocytes was confirmed in the second examination (1979). This increase, while statistically significant, was small (seen only in 11 of 194 workers) and had no apparent clinical importance, since mean values for all of the hematologic parameters analyzed were well within the standard range reported. The authors concluded that serum PCB levels were related to "marginal" increases in monocyte counts that might have been related to the use of different analytical methods to assess this parameter in the two examination periods. Consistent with these negative findings, Taylor[51] reported that PCB capacitor worker mortality from diseases of the blood and blood-forming organs was not significantly different from that expected based on national mortality rates.

Only three clinical surveys involving persons environmentally exposed to PCBs have reported analyses of hematological parameters. None of these studies found an excess of hematological abnormalities.[33-35]

While studies examining immunocompetence in individuals exposed to PCBs are quite limited, what evidence is available does not suggest that occupational exposures to PCBs were immunotoxic. First, there is no evidence from existing studies that PCB exposure adversely affects the levels of circulating immunocytes. In fact, leukocyte count and differential blood cell counts from six clinical studies found no association between PCB exposure and these parameters.[15,24,32,34,37,38] Second, Emmett et al[30] have recently compared 55 workers exposed to PCBs and 56 nonexposed persons with respect to hypersensitivity reactions as measured by dermal responses to mumps and trichophyton antigens and found no sig

nificant differences in the response frequencies of the two groups. Third, the clinical studies of PCB-exposed workers in general provide indirect evidence that occupational contact with PCBs does not result in immune system dysfunction. Exposed PCB workers have been consistently described as healthy overall, with no evidence of increased frequency of infections or illnesses; and no association has been found between PCB exposure and an excess mortality from infectious diseases.[31]

Effects on the Kidneys

Several clinical studies of PCB-exposed populations have included tests for renal dysfunction or damage. The tests most commonly included were blood urea nitrogen (BUN) and creatinine measurements, although other indices were occasionally analyzed. No study found evidence for an association between PCB exposure and renal toxicity or kidney disease. The infrequent abnormalities noted in some of the studies of larger worker populations lack control groups for comparison.[23,24] These low frequencies do not appear to be greater than would be anticipated in a healthy population. Lawton et al[23] reported increases in mean urinary specific gravity and serum osmolarity, as well as a greater than expected prevalence of cells in the urine, but stated that methodological deficiencies (failure to obtain "clean catch" urine samples) and the historical prevalence of diabetes and urinary tract problems (kidney stones [4.1%] and urinary tract infections [7.2%]) among the workers may explain these findings independently of PCB exposure. Supporting evidence for the lack of significant findings in the clinical studies is the fact that mortality from genitourinary diseases such as nephritis is not significantly elevated among US capacitor workers.[31]

In a study of potential PCB exposure via environmental contamination, Stehr-Green et al[33] reported weak statistical correlations between log serum PCB levels and both uric acid ($P = .08$) and BUN ($P = .05$). However, mean values for these parameters fell within the expected ranges and the authors failed to associate any increase in physician-diagnosed urinary tract problems with increased serum PCB levels. Stark et al[34] reported transient changes in serum electrolytes (slightly increased potassium and decreased phosphorus) in people exposed to a transformer fluid spill, but BUN, uric acid, and creatinine were unaffected and serum electrolytes were normal at the 6-week follow-up examination. Nethercott and Holness[35] similarly found no changes in BUN or serum creatinine in sewage treatment workers potentially exposed to PCBs.

Effects on the Gastrointestinal Tract

Detailed evaluations of potential gastrointestinal effects of human exposures to PCBs are currently unavailable. However, none of the clinical or mortality studies to date have noted an increased occurrence of gastric ulcer or other nonmalignant gastrointestinal diseases among PCB-exposed workers.[31,34] In the clinical investigations of PCB-exposed workers, the incidence of nonspecific complaints possibly relating to gastrointestinal function was reported,[15,24,30,38] but no clear association with PCB exposure or a specific clinical effect was identified. Queries about gastrointestinal symptoms in other occupational cohorts[23,37,39,41] or after environmental exposures to PCBs[31–34] apparently revealed no excess complaints or associations with PCB body levels.

Effects on the Nervous System

The current human evidence suggests that PCB exposure is not associated with clinical impairment of the nervous system. Although some associations between exposure and increased rates of subjective symptoms have been made, the meaning of subjective symptoms in the absence of objective clinical signs with regard to chemical exposure is always difficult to interpret. In the case of PCBs, subjective symptoms have been generally inconsistent with medical histories, physical examination findings, and measures of PCB exposure. For example, Fischbein et al[24] reported an apparently high prevalence (158/326) of subjective neurological symptoms, primarily the common complaints of headache, nervousness, or fatigue among PCB capacitor workers. However, none of the subjective symptoms was related to duration of employment or serum PCB level, and the authors noted that, "*routine neurological examination did not reveal any remarkable prevalence of abnormalities.*" Similarly, Smith et al[38] reported the results of a questionnaire given to PCB-exposed workers in which complaints of "loss of appetite" and "tingling in the hands" were statistically correlated with log serum PCB concentrations "in the presence of confounders." These confounders apparently could not be excluded from the analysis, and the meaning of these responses is impossible to determine without further investigation. Though physical signs of neurotoxicity were not specifically discussed by the authors, Smith et al[38] stated "*No consistent patterns of abnormalities were noted on physical examination at any study site.*" Finally, while Emmett et al[30] reported higher rates of subjective symptoms (headache, loss of appetite, insomnia, and memory trouble) in transformer repair workers, these investigators found no corresponding excess of neurologic abnormalities in the medical histories or physical examinations of these workers.

In summary, a number of occupational studies have failed to find any excess neurological deficits related to PCBs after performing complete physical examinations and/or medical history analyses.[15,18,19,23,32,37,41] Consistent with the negative findings of these clinical studies, the mortality analyses have not revealed any significant excess of deaths from nervous system diseases among PCB capacitor workers.[26,49,51]

Effects on Endocrine Function

The potential effects of PCB exposure on endocrine function have only been investigated to a limited extent in the clinical studies reported to date. No untoward effects on thyroid function were found in studies measuring serum T3 and/or T4 levels or on the prevalence of thyroid-related abnormalities.[29,39] Likewise, no evidence of a PCB-induced effect on the pancreas

creas has been observed. Lawton et al[23] reported that five of 40 elevated blood glucose measurements during two clinical examinations of capacitor workers were probably related to diabetes while the remainder were apparently due to testing inconsistencies and/or methodological problems. Stehr-Green et al[33] reported that mean blood glucose and the relative risk of elevated blood glucose were not significantly altered in people with >20 ppb serum PCBs, although a weak trend in increase was observed. Smith et al[38] and Emmett et al[29] observed no alterations in blood glucose measurements among capacitor and transformer repair workers. Confirming the lack of endocrine effects reported in the clinical studies, no mortality study has revealed any excess of deaths related to endocrine organ effects, such as diabetes mellitus or pancreatitis. In fact, Taylor[41] specifically reported a lower than expected mortality from allergic, endocrine, metabolic, and nutritional diseases, and from diabetes. While the present data are limited, there is no evidence that PCB exposure results in endocrine dysfunction or disease of any kind in occupationally or environmentally exposed persons.

Conclusions

Studies of PCB-exposed populations collectively suggest that the only adverse health effects attributable to PCBs in humans are dermal: chloracne, hyperpigmentation, and sequelae of chronic dermal and ocular irritation. These conditions occurred only in worker populations with relatively high dermal and/or inhalation exposures. PCB-related dermal effects have not been clearly identified among worker populations receiving lesser exposure and were absent in populations environmentally exposed to PCBs through the consumption of contaminated fish, by living near PCB waste sites, or by potential contact with PCB-contaminated soils. The assignment of PCBs as the causative agent for chloracne among workers with high PCB exposures is only tentative. Reported incidences of chloracne were typically greatest for occupational environments in which PCBs were used as heat transfer fluids, raising the possibility, as was the case with Yusho and Yu-Cheng, of unusually high levels of contamination with potently chloracnegenic PCDFs. The relationship between PCB body burdens and chloracne is not necessarily consistent with PCBs as causative agents—chloracne was only found in workers with high body burdens of PCBs, but many workers with very high body burdens did not develop chloracne. In the absence of measurements of PCDF levels in these studies, a causative or contributing role of PCDFs in chloracne among PCB-exposed workers cannot be ruled out.

The collective occupational experience with PCB fluids provides no evidence for adverse effects for other organ systems, including the liver, the heart and circulatory system, the gastrointestinal and urinary tracts, the nervous system, the respiratory system, the immune/hematopoietic system, and some endocrine functions. The absence of adverse effects in humans despite a variety of toxic effects of PCBs demonstrated in animal studies is consistent with the conclusions of other recent reviews of PCB toxicology.[55–58] This divergence in the findings reported for animal and human studies may result from many factors including species differences in susceptibility or sensitivity to PCB effects, as well as dosages tested in animal studies that were far greater than those found in even the highest of the occupational exposures. Confidence in the apparent absence of PCB-related diseases in humans is strengthened by the observation that this information is based primarily on studies of individuals with chronic, very high exposures to PCBs in industries where PCB use spanned over a 50-year period. With the strictly regulated use and disposal of these chemicals, it is unlikely that human exposures to PCBs will ever again match those of workers in previous decades. Therefore, it would appear that there is little basis for concern for organ system toxicity, at least among the broad categories covered in this review, resulting from present day exposures to these compounds.

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Whales Again in Danger

The story of man's exploitation of the world's great whales is both short and bloody. In the space of just 300 years, thriving populations of whales were brought to the brink of extinction. As each species was all but wiped out, the whalers turned their attention to others. By 1986, when a world moratorium on commercial whaling was at last introduced, few species survived in sufficiently large numbers to be worth exploiting. The minke whale was one exception. Japan has carried on killing significant numbers of minke whales in the Antarctic under the premise of so-called "scientific" whaling.

Despite Japan's obvious flouting of the International Whaling Commission's ruling, the 1986 moratorium was a major victory for those countries which wanted to see commercial whaling stop, many of whom had joined the IWC with that aim in mind. Sadly, the IWC now looks certain to collapse, and when it does, commercial whaling seems sure to resume. To understand why the IWC is in danger of demise, it is essential to look at its history. It was created in 1946, by the whaling countries, in a bid to administer regulations for the exploitation and conservation of whale stocks. It took over its role from the League of Nations which, in 1937, had made the first efforts to control the whaling industry. The basis of the IWC has always been the assumption that commercial whaling is acceptable. That is understandable, when it is remembered that the IWC was set up by whalers for whalers. During the 1970s and 1980s, many countries joined the IWC because they believed that the organization was more interested in setting quotas for kills, rather than conserving stocks. It was due to the influence of these countries that the 1986 moratorium was introduced.

The whaling nations agreed to the moratorium only on the basis that there would be a thorough assessment of whale stocks, and that, if certain populations were found to be large enough, commercial whaling could recommence. But recent years have seen a marked change in world opinion: the justification for whaling has at last been questioned.

There is now a rift of interest within the IWC. The majority of members are unlikely ever to approve of the resumption of commercial whaling. This has led Iceland to announce its withdrawal, with Norway and Japan, the other remaining whaling nations, likely to follow suit. . . .To leave the IWC and resume whaling would bring diplomatic isolation and international condemnation to the countries concerned, but they may feel that it is a price worth paying, even with the possibility of US trade sanctions. Although international trade in whale products is banned under the Convention of International Trade in Endangered Species (CITES), it should be noted that Iceland has never joined CITES, and Norway and Japan maintain reservations on several whale species, and are thus not restricted by CITES either. Being unable to trade in whale products would not bother the Japanese, as home demand for whale meat is strong. . . .

There is no questioning the cruelty of whaling: killing an animal as large as a whale is exceedingly difficult. . . .In a world where humanitarian interests continue to gain support, the whole question of the morality of whaling is being challenged. None of the countries which wish to resume whaling have any reason to do so apart from financial gain. . . . Here is a real chance for the European Community (EC) to demonstrate its economic power and inflict trade embargoes on all three nations if they decide to resume whaling. Norway and Iceland would surely take notice of a blockade, for their economies are closely intertwined with the EC. If the public makes its views known, . . . then there is a strong possibility that whaling will, at last, be halted.

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