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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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[52]	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[49]	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[50]	Mortality analysis (188 deaths)	788
		Brown, 1987[49]	Mortality analysis (116 deaths)	981
		Taylor, 1988[51]	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-

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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

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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)[16] 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.

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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-

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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[51] 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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