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Evaluation of Potential Health Effects Associated with Serum Polychlorinated Biphenyl Levels

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In late 1983, we conducted a cross-sectional epidemiologic study to evaluate persons at risk of exposure to three chemical waste sites by comparing clinical disease end points and clinical chemistry parameters with serum polychlorinated biphenyls (PCB) levels. A total of 106 individuals participated in the study. The only statistically significant finding in regard to self-reported, physician-diagnosed health problems was a dose-response relationship between serum PCB levels and the occurrence of high blood pressure; however, this association failed to achieve statistical significance ($p = 0.08$) when we controlled for possible confounding effects of both age and smoking. Serum triglyceride and cholesterol levels were also higher in the group with elevated serum PCBs; additionally, there were isolated statistically significant correlations of serum aspartate aminotransferase (SGOT) with serum lipid fraction-adjusted PCB level ($r = -0.21$) and serum albumin ($r = -0.24$) and total bilirubin ($r = 0.30$) with serum PCB level. Although the ranges of serum levels reported herein from exposures to PCBs in the general environment are lower than those that have been associated with acute symptoms or illness in other studies, whether these levels are associated with long-term health risks is not known. Associations of such chronic, low-dose exposures with observable health effects as suggested by this study must be evaluated further before any final conclusions can be drawn.

Background

Bloomington, a city of 53,000 (1980 census) in Monroe County, IN, has a complicated history of industrial waste disposal compounded by unusual geologic features that make the environment susceptible to pollution by such wastes. In late 1983, the Indiana State Board of Health, in consultation with the Centers for Disease Control (CDC), initiated a cross-sectional epidemiologic study of exposure to and health effects from polychlorinated biphenyls (PCBs) among residents near three chemical waste sites. Primarily, we intended to evaluate persons at high risk of exposure to these waste sites to determine if any of these individuals have abnormally elevated serum PCB levels and to identify which environmental pathways containing PCBs might have contributed most to producing abnormally elevated levels of PCBs in human sera. A more detailed site history and the results of these analyses are discussed in another report (*1*). Secondarily, we intended to compare clinical disease end points and clinical chemistry parameters with serum PCB levels; this report is a summary of those findings.

Materials and Methods

We selected participants on the basis of screening questionnaire data collected on all persons who had resided within ½ mile of the three waste sites for at least 5 years. Since the primary purpose of the study was to evaluate persons at high risk of exposure to these waste sites, we first selected five to ten persons with the highest risk of exposure (i.e., with the greatest lifetime number of exposure opportunities) through each of several environmental pathways—e.g., eating contaminated native fish, playing or working in contaminated soil areas. We also selected a group of participants who reported having had no occupational PCB exposures or exposures to the waste sites. Finally, we selected a group of persons by computer-generated random numbers from the universe of 995 persons identified in the screening survey.

We attempted to contact persons selected for the study in person or by telephone on at least three different occasions. Any person who was unwilling or unable to participate, or who was classified as lost to fol-

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low-up, was replaced by the next eligible person until we had recruited the sought-after number of participants in each category or until we had exhausted the list of eligible persons. If the subjects were still willing to participate, they were asked to fast for 12 hr before their appointments for interview and phlebotomy. On the day of the appointment, after obtaining informed consent, 1 of 12 trained interviewers administered a questionnaire to each participant that included items on demographic characteristics, prescription drug use, and history of selected conditions or diseases which had been evaluated/diagnosed by a physician. In addition, we collected fasting blood specimens (30 mL for adults and 15 mL for children) using equipment and supplies, including Vacutainer tubes, Wheaton vials, and Pasteur pipettes (all either hexane-rinsed or determined to be free of PCBs by previous tests of blank tubes). Blood was allowed to clot for 30 to 50 min and was then centrifuged for 10 to 20 min. Serum was pipetted into Wheaton vials, which were then placed immediately on ice and kept frozen and under strict chain of custody surveillance until CDC laboratory personnel opened them.

Serum PCB levels were determined by the method of gas chromatography with electron capture (*2*). Quality assurance and quality control were strictly monitored by analyzing bench, blind, blank, and interference controls and blind split duplicates with each analytical run. Participants' sera were also analyzed for a 16-analyte, liver-function profile run on a DuPont Automatic Clinical Analyzer (ACA III). The analytes included: gamma glutamyl transferase, aspartate aminotransferase (SGOT), triglyceride, cholesterol, alkaline phosphatase, total bilirubin, conjugated bilirubin, lactic dehydrogenase, urea nitrogen, albumin, total protein, alanine aminotransferase (SGPT), uric acid, glucose, high-density lipoprotein cholesterol, and immunoglobulin G. Age- and sex-specific reference ranges for normal individuals were supplied by the manufacturer of the ACA III.

Categorical data (e.g., measurements with a low expected proportion of positive results such as abnormally elevated serum cholesterol levels) were examined via a contingency table approach (χ^2 analysis) to determine if differences existed between groups by using statistical results for "normal" ranges specific to the laboratory and equipment employed in the analysis. When appropriate, parametric statistics (e.g., analyses of variance, *t*-tests for means) were used to compare group means for serum analyte levels. To examine possibly interactive and/or confounding associations, we used multivariate techniques, such as analyses of correlation and logistic regression modeling, using *a priori* reasoning on variables to be included.

Since the serum levels of PCBs and selected analytes were lognormally distributed, all statistics are based on these log-transformed values. Further, although the total number of participants was 106, many of the analyses discussed below were conducted with a data set comprising slightly less than the total sample, because of missing values for either laboratory results or one or more of the various demographic variables.

Table 1. Estimated excess prevalence of self-reported, physician-diagnosed health problems by serum PCB level: Bloomington, IN, 1984.

	Relative risk (*p*-value)		
Organ system or diagnostic entity	≥ 20 ($N=20$) vs. < 20 ppb ($N=94$)	≥ 30 ($N=9$) vs. < 30 ppb ($N=105$)	≥ 40 ($N=5$) vs. < 40 ppb ($N=109$)
Liver	1.57 (0.43)	1.67 (0.49)	3.12 (0.31)
Urinary	0.78 (0.42)	0.43 (0.30)	0.81 (0.64)
Skin	1.14 (0.43)	0.92 (0.59)	1.12 (0.59)
Neurological	1.22 (0.38)	0.73 (0.46)	1.36 (0.47)
Eye	1.88 (0.21)	0.90 (0.70)	0.00 (0.51)
Respiratory	0.75 (0.58)	0.86 (0.59)	0.78 (0.62)
Generalized problems	0.72 (0.58)	0.83 (0.56)	1.56 (0.40)
Cancer	0.00 (0.58)	0.00 (0.66)	0.00 (0.80)
High blood pressure	1.63 (0.17)	1.73 (0.20)	2.34 (0.12)

Results

Of the 106 participants from whom we elicited medical histories, 82 (77.4%) had self-reported, physician-diagnosed health problems for at least one of the 50 conditions listed on the questionnaire. Similarly, 80 (75.5%) participants reported having been diagnosed with health problems in at least one of the nine selected target organ systems/conditions thought to be especially susceptible to the effects of PCB exposure (i.e., high blood pressure, liver disease, urinary tract disease, dermatologic problems, eye problems, neurological disorders, respiratory problems, cancer, and selected metabolic disorders).

There were no statistically significant differences in the prevalence of any of these self-reported health outcome variables between the 20 persons with serum PCB levels ≥ 20 ppb)* and the remaining 86 persons in the study population with serum PCB levels < 20 ppb (see Table 1). To elucidate possible dose-response relationships, we conducted a series of analyses comparing the health outcomes of persons with ≥ 20, 30, and 40 ppb of PCBs in serum with those whose serum levels were lower than each of these respective cutoffs. A review of these qualitative results suggests a serum PCB level-response gradient for liver problems, high blood pressure, and generalized disorders. When all health outcomes were evaluated using logistic regression, only the model with high blood pressure as the dependent variable was statistically significant ($p < 0.05$); the contribution of serum PCB level to the model was also significant ($p < 0.05$). This significance remained even when the model was controlled individually for age or smoking (i.e., average number of cigarettes per day).

*From previous results of statistical characterizations of population groups in Michigan and South Carolina (*3,4*), we would expect that 95% of any randomly selected population sample will have serum PCB levels < 20 ppb; thus, we arbitrarily classified serum levels of ≥ 20 ppb as "abnormally elevated."

Table 2. Correlation of log serum lipid fraction PCB level with selected clinical chemistry results: Bloomington, IN, 1984.

Serum analyte	N	r	p value
Aspartate aminotransferase	102	− 0.21	0.04
Triglyceride	105	− 0.04	0.70
Cholesterol	105	0.14	0.16
Total protein	104	− 0.06	0.51
Alanine aminotransferase	102	− 0.10	0.32
Glucose	102	0.06	0.58
High-density lipoproteincholesterol	102	− 0.06	0.56
Immunoglobulin G	88	− 0.10	0.33

When all variables were included together in the model, however, overall significance dropped ($p = 0.06$), as did the contribution of serum PCB level to the model ($p = 0.08$).

To gain a better understanding of the possible association of PCB exposure (as measured by serum PCB level) with the chosen clinical chemistry parameters, we examined serum analyte levels for 15 of the 16 analytes in subjects' sera for which sufficient specimen volumes were available; results for conjugated bilirubin levels were considered to be invalid because of laboratory quality control problems. We calculated correlation coefficients between log-transformed serum PCB levels and the serum analytes included in the ACA III analyses. Since the laboratory analytical techniques used for selected analytes can be affected by total serum lipids, we correlated these variables with serum PCB levels corrected for serum lipid fraction; results for these eight analytes are presented in Table 2. Only serum SGOT was statistically significantly inversely associated with serum lipid fraction-adjusted PCB level. Table 3 contains the results of analyses conducted for the remaining seven analytes. Serum albumin was statistically significantly inversely correlated, and total bilirubin was directly correlated with serum PCB level.

We also compared mean serum levels for these 15 analytes between those persons with serum PCB levels $\geq$ 20 ppb versus those with levels < 20 ppb on the clinical chemistry results (shown in Table 4). The only significant differences in mean analyte values were found for serum triglyceride and cholesterol. Similarly, persons with serum PCBs $\geq$ 20 ppb (see Table 5) had a significant relative risk of having abnormally elevated (i.e., ± 2 standard deviations from the age- and sex-specific reference laboratory "expected" or "normal" means) serum triglyceride (RR = 4.8, $p < 0.01$) and cholesterol (RR = 4.6, $p = 0.02$). All other differences were not statistically significant.

Table 3. Correlation of log serum PCB level with selected clinical chemistry results: Bloomington, IN, 1984.

Serum analyte	N	r	p value
Gamma glutamyl transferase	105	0.11	0.28
Alkaline phosphatase	105	− 0.12	0.21
Lactic dehydrogenase	102	− 0.01	0.88
Urea nitrogen	105	0.19	0.05
Albumin	105	− 0.24	0.02
Total bilirubin	105	0.30	< 0.01
Uric acid	103	0.17	0.08

To control for potential confounding, we performed logistic regression analyses for abnormal serum analyte values regressed on PCB levels and potential confounders (e.g., age and alcohol consumption). The only model that was statistically significant was one in which abnormally elevated serum glucose levels were regressed on lipid fraction PCB level, age, and alcohol consumption ($\chi^2[df=3] = 8.36$, $p = 0.04$)—with subject's age being the only independent variable contributing significantly to the model (directly associated, $p = 0.01$). Other models with an overall χ^2 statistic with $0.05 < p < 0.10$ were for: elevated SGOT regressed on lipid fraction PCB level (inversely associated, $p = 0.05$), age (directly associated, $p = 0.03$), and alcohol consumption ($p = 0.96$); elevated urea nitrogen regressed on serum PCB level (directly associated, $p = 0.06$) and age ($p = 0.88$); elevated SGPT regressed on lipid fraction PCB level (inversely associated, $p = 0.02$), age ($p = 0.15$), and alcohol consumption ($p = 0.14$); and elevated total bilirubin regressed on serum PCB level ($p = 0.25$), age ($p = 0.72$), and alcohol consumption (directly associated, $p = 0.06$).

Finally, we attempted to evaluate the degree to which the clinical chemistry results of these persons may reflect liver damage by convening a review panel of three physicians with postdoctoral training and clinical experience in internal medicine. The reviewers, who were "blinded" to the exposure status of the patients (i.e., *a priori* groupings and serum PCB levels), were asked to make a clinical judgment on each patient in regard to the presence of "possible (or probable) liver disease which would require follow-up clinical evaluation" on the basis of review of the laboratory slips. In all, 14 patients were judged by at least two of the three reviewers to have "possible liver disease." Of those with serum PCB levels $\geq$ 20 ppb, 21.1% (4/19) were so classified as showing signs consistent with possible liver disease versus 11.5% (10/87) of those with serum PCB levels < 20 ppb. This corresponds to a relative risk of 1.62, which was not statistically significant ($p = 0.22$).

Discussion

The evidence for a direct association of serum PCB level with hypertension is perhaps the most significant finding of this study. Health effects reported for workers exposed to PCBs have not included this association but have recorded excess prevalence of chloracne and other skin irritations, digestive disturbances, eye irritation, and impotence (*5*). However, in one study of nonoccupationally exposed persons who ate fish contaminated with PCBs, an association between serum PCB level and diastolic blood pressure was demonstrated which persisted after potentially confounding variables, including age, were taken into account (*6*). Consistent with this previous report and others in the literature, our data support a dose-response relationship of serum

Table 4. Mean clinical chemistry results by serum PCB level: Bloomington, IN, 1984.

Analyte	Unit of measure	Mean values (standard deviation) ≥ 20 ppb serum PCB	N	< 20 ppb serum PCB	N	t-test
Gamma glutamyl transferase	U/L	28.7 (25.7)	18	27.6 (28.7)	87	(p = 0.88)
Aspartate aminotransferase	U/L	36.0 (7.8)	15	38.2 (12.3)	87	(p = 0.50)
Triglyceride	mg/dL	264.9 (21.9)	18	129.7 (71.5)	87	(p = 0.02)*
Cholesterol	mg/dL	245.1 (55.0)	19	190.9 (46.3)	87	(p < 0.01)†
Alkaline phosphatase	U/L	105.7 (33.7)	18	105.9 (57.6)	87	(p = 0.98)
Lactic dehydrogenase	U/L	125.6 (24.5)	16	133.1 (33.9)	86	(p = 0.40)
Urea nitrogen	mg/dL	14.4 (6.0)	18	12.9 (3.6)	87	(p = 0.32)
Albumin	g/dL	4.3 (1.0)	18	4.4 (0.3)	87	(p = 0.17)
Total protein	g/dL	6.5 (0.7)	17	6.9 (0.6)	87	(p = 0.16)
Alanine aminotransferase	U/L	14.6 (5.6)	16	14.8 (8.4)	86	(p = 0.98)
Total bilirubin	mg/dL	1.2 (1.5)	18	0.7 (0.4)	87	(p = 0.10)
Uric acid	mg/dL	5.8 (1.6)	18	5.3 (1.5)	85	(p = 0.27)
Glucose	mg/dL	118.0 (42.9)	18	103.3 (38.6)	85	(p = 0.15)
High-density lipoprotein-cholesterol	mg/dL	38.1 (9.2)	16	40.4 (12.0)	86	(p = 0.47
Immunoglobulin G	mg/dL	1073.3 (209.7)	15	1072.2 (211.6)	74	(p = 0.99)

*Different from group with serum PCB ≥ 20 ppb at 5% level of significance.
†Different from group with serum PCB ≥ 20 ppb at 1% level of significance.

Table 5. Estimated excess prevalence of abnormal clinical chemistry results by serum PCB level Bloomington, IN, 1984.

Laboratory analyte	Relative risk ≥20 ppb vs. ≤20 ppb serum PCB	N
Gamma glutamyl transferase, elevated:[a]	0.94 (p = 0.70)	97
Aspartate aminotransferase, elevated:	1.52 (p = 0.30)	94
Triglycerides		
Elevated:	4.83 (p < 0.01)	105
Decreased:[b]	0.00 (p = 0.69)	105
Cholesterol		
Elevated:	4.57 (p = 0.02)	106
Decreased:	0.00 (p = 0.45)	105
Alkaline phosphatase, elevated:	0.81 (p = 0.56)	105
Lactic dehydrogenase, elevated:	0.00 (p = 0.35)	102
Urea nitrogen, elevated:	9.66 (p = 0.08)	105
Albumin, decreased;	NC[c] (p = 1.00)	105
Total protein, decreased:	1.71 (p = 0.20)	104
Alanine aminotransferase, elevated:	0.00 (p = 0.50)	102
Total bilirubin elevated:	4.83 (p = 0.06)	105
Uric acid, elevated:	1.72 (p = 0.16)	95
Glucose		
Elevated:	2.02 (p = 0.10)	103
Decreased:	0.00 (p = 0.83)	103
High-density lipoprotein-cholesterol		
Elevated:	0.00 (p = 0.84)	94
Decreased:	1.50 (p = 0.15)	94
Immunoglobulin G		
Elevated:	1.23 (p = 0.61)	89
Decreased	NC (p = 1.00)	89

[a] > 2 standard deviations above reference laboratory mean value.
[b] < 2 standard deviations below reference laboratory mean value.
[c] No cases in both study groups.

PCB levels and the occurrence of high blood pressure. The pathophysiology of this relationship, whether operating through PCB effects on renal function or enhanced progression of atherosclerotic processes, remains unclear. This association should be further evaluated in animal toxicologic studies, as well as in larger epidemiologic studies of actual measured blood pressures in which potentially important confounding factors (such as dietary habits and socioeconomic status) can be adequately controlled.

Other studies have shown an elevation of serum cholesterol, triglyceride, and high density lipoprotein with elevated serum PCB levels (*5,7,8*). Consistent with these studies, we found evidence of higher mean levels, as well as a greater prevalence of clinically elevated serum triglyceride and cholesterol in the group with serum PCB levels ≥ 20 ppb. These results may offer further evidence for an alteration in lipid metabolism due to PCB exposures. However, the results may be spurious because persons with elevated serum lipids due to other, unrelated factors may be more likely to have higher measured serum PCB levels because of the lipophilic nature of PCBs (*9*). In addition, because of limitations of the relatively small sample size and the unavailability of pertinent data, we could not control for all potentially important confounders.

Results of several studies of occupationally exposed persons have shown a direct association between serum PCB levels and gamma glutamyl transpeptidase and SGOT and an inverse association with bilirubin (*10*); these studies apparently show that PCBs are inducers of microsomal enzymes in man, but do not show conclusively that they cause liver damage. We could not corroborate these results with the data collected in this study. In fact, the inverse correlation of serum PCB

level with SGOT which we found contradicts these previous animal toxicological and human studies; however, this finding is biologically implausible except in cases of gross hepatic pathology, which we did not observe. Similarly, our finding of a statistically significant direct correlation of total bilirubin with serum PCB levels is probably spurious. The other statistically significant clinical chemistry findings—i.e., the direct correlation between serum PCB levels and serum uric acid levels, as well as the inverse correlation of serum albumin with serum PCB levels, are consistent with liver disease but were not corroborated in further analyses.

Summary and Conclusions

In summary, our results were suggestive of an increased risk of hypertension and altered lipid metabolism in persons exposed to environmental PCBs. Otherwise, we found no evidence of adverse health effects in other key target organs that included the skin and the nervous system. Similarly, no clear patterns of clinical pathology are evidenced from the clinical chemistry results. Our failure to demonstrate a significant excess of adverse health effects due to PCB exposure may have been due to the relatively small sample size in this study (i.e., low statistical power), our inability to detect effects with long latency periods, or missed subtle health effects or symptoms that had not been diagnosed by a physician (and, therefore, not recorded); alternatively, it may be that there are no detectable adverse health effects from chronic, low-dose exposures to environmental PCBs.

The ranges of serum levels reported herein from exposures to PCBs in the general environment are lower than those that have been associated with acute symptoms or illness in other studies, usually in occupationally exposed cohorts; furthermore, whether these levels are associated with long-term health risks is not known. The apparent overall lack in this study of positive associations of such chronic, low-dose exposures with observable health effects (with the possible exception of increased risk of high blood pressure and altered lipid metabolism) must be evaluated further before any conclusions can be drawn. Because of this uncertainty, the need continues for appropriate remedial action to prevent further exposure to this and other similar populations.

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