Determinants of Serum Polychlorinated Biphenyls and Organochlorine Pesticides Measured in Women from the Child Health and Development Study Cohort, 1963–1967

Rebecca A. James,[1] Irva Hertz-Picciotto,[1] Eric Willman,[2,] Jean A. Keller,[1] and M. Judith Charles[2]*

[1]Department of Epidemiology, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, USA; [2]Department of Environmental Toxicology, University of California-Davis, Davis, California, USA

We examined predictors of organochlorine concentrations in serum specimens from women who were pregnant in the 1960s and participated in the Child Health and Development Study in the San Francisco Bay Area of California. That study enrolled pregnant women at the Kaiser-Permanente Medical Facilities, conducted interviews, and drew blood specimens; these specimens were centrifuged and the resulting serum specimens were frozen and placed in long-term storage. For the current investigation, organochlorines were measured by dual-column GC-electron capture detection in specimens collected in 1963–1967 from 399 pregnant women during the second and third trimesters. Using multiple linear regression models adjusted for serum lipids, we evaluated factors predicting concentrations of 11 polychlorinated biphenyl (PCB) congeners, their sum, and several pesticides and metabolites. Variables evaluated were age, race, place of birth, date of blood draw, body mass index, occupation, past residence on a farm, parity, and duration of pregnancy at blood draw. Concentrations of highly chlorinated PCBs and the sum of the PCBs increased with age. Concentrations of certain PCB congeners, as well as the sum, were significantly higher among nonwhites and increased with calendar date of blood draw. *p,p′*-DDT and *p,p′*-DDE concentrations were about 50% higher for nonwhites compared with whites and for those born in California or the southeastern United States versus elsewhere in the United States. Higher body mass index was associated with lower concentrations of several PCBs and *p,p′*-DDE but with higher heptachlor epoxide and DDT levels. The increase in use of PCBs during the 1960s is apparently detectable as increasing concentrations in maternal sera between 1963 and 1967. Marked racial and regional differences in serum pesticide levels were likely caused by geographic variation in previous agricultural and vector-control uses. The relationship to body mass index appears to be complex. *Key words:* body mass index, Child Health and Development Study, DDE, DDT, heptachlor epoxide, organochlorines, pesticides, polychlorinated biphenyls. *Environ Health Perspect* 110:617–624 (2002). [Online 14 May 2002]
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Concern over developmental toxicity from human exposures to organochlorines stems from the biological and environmental persistence of these compounds and from adverse health and developmental effects observed in both experimental and epidemiologic studies. In the present study we examined predictors of serum polychlorinated biphenyl (PCB) and pesticide concentrations in archived specimens from a historical cohort of women who were pregnant in the 1960s.

PCBs, a class of 209 individual compounds (congeners), were introduced in the United States in the 1930s and marketed by their U.S. manufacturer as commercial mixtures with the trade name Aroclor (*1*). U.S. production of PCBs peaked in the early 1970s and ceased in 1977. Their chemical stability led to widespread industrial use in transformers and capacitors, as plasticizers, heat transfer fluids, hydraulic lubricants, adhesives, organic diluents, pesticide extenders, and cutting oils, as well as in carbonless reproducing paper and flame retardants (*2*). Although production has stopped in the United States and in most other parts of the world, PCBs are ubiquitous pollutants due to their persistence in the environment. On a global basis, redistribution of PCBs occurs by environmental transport and deposition processes and by inappropriate disposal practices. Bioaccumulation of PCBs through the food chain has resulted in high concentrations of PCBs in meat, milk, and fish, with present-day exposures primarily attributed to the ingestion of fish and to breast-feeding (*3*). Because of their lipophilic properties, PCBs are not readily cleared from the body. Estimated half-lives of individual PCB congeners in humans range from < 1 month to > 40 years (*4*). Those congeners that are more highly chlorinated, as well as those that have adjacent substituted carbon atoms at the *ortho* and *meta* positions of the biphenyl ring, tend to have longer half-lives (*5,6*). For example, half-life estimates for PCBs 101, 138, and 180 are as high as 8, 40, and 13 years, respectively (*4*).

Heptachlor epoxide is an oxidation product of heptachlor, an insecticide that was used to control termites and other insects during the 1960s and 1970s. Heptachlor was applied in homes and to seed grains and crops. Metabolism by plants, microbes, and animals (including humans) produces heptachlor epoxide. Ingestion of contaminated food and misapplication of heptachlor in homes were primary exposure routes. People whose homes were treated in the past can be exposed to dustborne heptachlor epoxide over an extended period. Because heptachlor epoxide bioaccumulates through the food chain, fish, milk, and meat products are other potential sources of exposure. Heptachlor epoxide can also be transmitted from mother to infant through breast-feeding (*7*).

DDT (dichlorodiphenyltrichloroethane) was used as a pesticide in agricultural and vector-control applications, with peak usage during the early 1960s (*8*). Preparations typically contained primarily *p,p′*-DDT with some *o,p′*-DDT. Both *p,p′*-DDT and *o,p′*-DDT have half-lives of about 7 years (*9*), while their DDE (dichlorodiphenyldichloroethylene) metabolites persist much longer (*8*). Measured concentrations of DDE are therefore greater in human biological samples than are concentrations of DDT (*10*). Although use of DDT was restricted in the United States in 1972 and finally banned in 1979 (*11*), previous extensive application worldwide, continued use in vector-control programs in developing countries, and environmental persistence of DDE have resulted in continued redistribution of these chemicals in the environment (*8*). Similar to PCBs and heptachlor epoxide, these compounds bioaccumulate, and primary

Address correspondence to I. Hertz-Picciotto, Department of Epidemiology & Preventive Medicine, TB #168, University of California, Davis, CA 95616 USA. Telephone: (530) 752-3025. Fax: (530) 752-3239. E-mail: ihp@ucdavis.edu

*Current address: Barnstead/Thermolyne Corp., Dubuque, Iowa, USA.

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routes for human exposure are meat and fish ingestion for adults and mother's milk for children (*10*).

In this study we measured total and congener-specific serum PCBs, *p,p′*-DDT, *p,p′*-DDE, *o,p′*-DDT, *o,p′*-DDE, and heptachlor epoxide in pregnant women from the Child Health and Development Study (CHDS). Because the CHDS was conducted during the 1960s, a time of peak usage and production of these organochlorines, we expected body burdens to be higher than those found in general population studies conducted more recently in the United States and other developed countries. To better understand determinants of the CHDS population's body burdens of these organochlorines during this time period, we examined serum concentrations in relation to a number of social, demographic, and reproductive factors.

Materials and Methods

Study population. The CHDS is a prospective cohort study that enrolled about 20,500 pregnant women attending prenatal clinics at Kaiser Foundation Health Plan Medical Centers in the San Francisco Bay Area of California during the 1960s (*12*). The Kaiser Health Plan, a prepaid health maintenance organization, at that time had enrolled 90% of membership through employer or union groups (*13*). The population served was thus largely persons having stable employment, with wealthy and very poor persons generally not well represented. Otherwise, members represented a broad cross-section of the San Francisco Bay Area population.

The 399 women in this study are a sample from the original CHDS cohort. They were selected from a subset of 3,400 women whose children underwent an extensive examination at 5 years of age. By CHDS design, eligibility criteria for this group were residence in the San Francisco Bay Area at 5 years of age; mother not an unmarried minor at time of pregnancy; and child born between April 1964 and April 1967. Before sampling for the current study, we excluded women who completed the enrollment interview after delivery, whose interview was incomplete, or for whom a second or third trimester blood specimen was not drawn or an insufficient amount of serum was available. Because we were ultimately interested in evaluating hypothyroid effects and early developmental outcomes, the current study further excluded *a*) children with severe anomalies and those who did not complete two cognitive exams, a hearing exam, and a speech exam; *b*) mothers who were deaf, had rubella during pregnancy, were taking thyroid medication in the 60 days prior to blood draw, or took iodine-containing medication during pregnancy or in the 6 months prior to conception; and *c*) infants born at less than 35 or greater than 45 completed weeks of gestation or for whom gestational age was unknown. Where mothers had more than one eligible child, no more than one was randomly selected.

We then selected a limited group of counties, based on current residence, to enable follow-up of the adults. After these exclusions, there remained 1,291 children from whom we sampled all children whose standardized score on the Raven's Progressive Matrices or the Peabody Picture Vocabulary Test was below the 10th percentile, or who failed a hearing screening, and a 17% random sample of those who scored above the 10th percentile on both exams and passed the hearing screening. Serum PCB, *o,p′*-DDT, *p,p′*-DDT *o,p′*-DDE, *p,p′*-DDE, heptachlor epoxide, and lipid levels were ascertained for 399 women in this final sample, which included mothers of 182 children who had low cognitive scores, 46 who failed the hearing screening, 12 who both had low cognitive scores and failed the hearing screening, and 159 among the others.

Data collection and coding of variables. In the CHDS, mothers' sociodemographic data and health and reproductive histories were collected in an interview during pregnancy and by abstraction of medical records. Most variables used in our analyses were taken from women's questionnaire responses in early or mid-pregnancy. Date of last menstrual period (LMP) was reported as month, day, and year of the LMP recalled. If month was known but exact day not specified, recollections of LMP at the "beginning of the month" were coded as the 7th of the month, at the "end of the month" as the 23rd, and not specified as the 15th. The duration of pregnancy at blood draw was calculated by subtracting the LMP date from the date of the draw.

Age was calculated by subtracting mother's reported year of birth from the year of delivery. Parity is the total number of reported previous liveborn infants; we categorized this variable as 0, 1–2, and ≥ 3 previous liveborn infants. Body mass index (BMI), in kilograms per square meter, was calculated from pre-pregnancy weight and height at the time of interview. We categorized place of birth as *a*) California, *b*) Southeast United States (includes Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia), *c*) United States other than California or the Southeast, and *d*) outside the United States. This last group was small; we therefore subsequently excluded those born outside of the United States (6.5% of sample) for analyses involving birthplace. The race variable was constructed from self-reported race and ethnicity. Because of the very low percentage in our sample of Hispanics (2.4%), Asians (4.2%), and multiple or other races (3.5%), we combined these groups with African Americans (hereafter designated "nonwhites"). If the woman reported having lived on a farm for more than 5 years before the age of 15, she was included in the farm residence during childhood category. Based on the distributions in our data, mother's occupation immediately before becoming pregnant was categorized into four groups: housewife; factory or household worker; secretary or clerical worker; and professional, teacher, or manager.

Laboratory methods. The blood specimens, drawn during pregnancy, were centrifuged, and the sera were aliquoted and stored at –20°C. Specimens collected after April 1966 were stored locally and later shipped, frozen, to a National Institutes of Health (NIH) storage facility in Frederick, Maryland; samples collected earlier were sent directly to NIH storage facilities. The specimens were thawed, aliquoted, frozen, then shipped in dry ice to the University of California, Davis. The protocol for organochlorine determination was as follows: Samples were thawed and then homogenized with a vortex mixer. A 400-µL aliquot of each sample was vortexed with surrogate standards 2,3,4,4′-tetrachorobiphenyl (PCB 66) and 2,3,3′,5,5′,6-hexachlorobiphenyl (PCB 165) and allowed to equilibrate at room temperature. Glacial acetic acid (500 µL) was added, vortexed, and allowed to equilibrate. The mixture was

Table 1. PCB congeners considered at the outset of this study.

Congener no.	Name
49	2,2′,4,5′-Tetrachlorobiphenyl
52	2,2′,5,5′-Tetrachlorobiphenyl
70	2,3′,4′,5-Tetrachlorobiphenyl
77	3,3′,4,4′-Tetrachlorobiphenyl
99	2,2′,4,4′,5-Pentachlorobiphenyl
101	2,2′,4,5,5′-Pentachlorobiphenyl
105	2,3,3′,4,4′-Pentachlorobiphenyl
110	2,3,3′,4′,6-Pentachlorobiphenyl
114	2,3,4,4′,5-Pentachlorobiphenyl
118	2,3′,4,4′,5-Pentachlorobiphenyl
123	2′,3,4,4′,5-Pentachlorobiphenyl
126	3,3′,4,4′,5-Pentachlorobiphenyl
132	2,2′,3,3′,4,6′-Hexachlorobiphenyl
137	2,2′,3,4,4′,5-Hexachlorobiphenyl
138	2,2′,3,4,4′,5′-Hexachlorobiphenyl
153	2,2′,4,4′,5,5′-Hexachlorobiphenyl
156	2,3,3′,4,4′,5-Hexachlorobiphenyl
157	2,3,3′,4,4′,5′-Hexachlorobiphenyl
166	2,3,4,4′,5,6-Hexachlorobiphenyl
169	3,3′,4,4′,5,5′-Hexachlorobiphenyl
170	2,2′,3,3′,4,4′,5-Heptachlorobiphenyl
177	2,2′,3,3′,4′,5,6-Heptachlorobiphenyl
180	2,2′,3,4,4′,5,5′-Heptachlorobiphenyl
183	2,2′,3,4,4′,5′,6-Heptachlorobiphenyl
187	2,2′,3,4′,5,5′,6-Heptachlorobiphenyl
189	2,3,3′,4,4′,5,5′-Heptachlorobiphenyl

extracted three times with 90% hexane/10% dichloromethane. The combined extracts were reduced under a stream of pure nitrogen and purified on a 0.5% deactivated florisil column with 60 mL of hexane and then 60 mL of 50% hexane/50% dichloromethane. The eluants were combined and concentrated with a rotary evaporator, and internal standard 2,2′,3,4,4′,5,6,6′-octachlorobiphenyl (PCB 204) was added. Serum specimens were analyzed by gas chromatography (Hewlett-Packard 6890 Series; Hewlett-Packard, Palo Alto, CA) with electron capture detection using an RTX-5MS and an RTX-1701 column run simultaneously in the same GC. The columns have different polarity and therefore increased the number of completely resolved congeners in these samples. A detailed description of laboratory methods and quality assurance and quality control procedures has been published (*14*).

We measured triglycerides and total cholesterol by standard enzymatic technique (*15–17*) using a Hitachi 911 automated analyzer from Boehringer Mannheim (Roche, Indianapolis, IN). We estimated total lipids by applying the following formula: Total lipids= (2.27 × Total cholesterol) + Triglycerides + 0.623 (*18*). This formula provides an estimate of phospholipid contribution to total lipids; however, this approach introduces some error because an individual's phospholipid serum fraction will vary by individual factors such as age, BMI, health status, and whether or not the sample was taken after a fasting period.

Before analyzing any samples from our subjects, we analyzed noncritical samples from the same cohort (i.e., of women in CHDS who were lost to follow-up) to assess the integrity of the stored serum specimens. Organochlorine determinations demonstrated comparability with other historical samples, and lipids were in reference ranges. Samples analyzed on batch dates with extremely high or low variability were reanalyzed, and the two values were averaged.

At the outset of the study, we identified the congeners listed in Table 1 as having been associated with developmental outcomes in prior experimental studies either individually or as part of an Arochlor mixture. *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDT, *p,p′*-DDT, and heptachlor epoxide were also analyzed. Using the relative standard deviation (*14*) and the methods of Gibbons et al. (*19*), we identified and excluded from our current analyses those PCB congeners that were consistently below the limit of quantification (LOQ), or which coeluted. PCB congeners 49, 52, 70, 77, 114, 123, 126, 132, 157, 166, 169, 177, 183, and 189 were sufficiently resolved on one or both columns but were consistently below the limit of quantitation. PCB 99 coeluted with endosulfan I on the 5MS column and *o,p′*-DDE on the 1701 column and so could not be analyzed. PCB 77 coeluted with PCB 110 on the 5MS and was below the limit of detection on the 1701 column. Here we report results for PCB congeners 101, 105, 110, 118, 137, 138, 153, 156, 170, 180, and 187, as well as *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDT, *p,p′*-DDT, and heptachlor epoxide. For those organochlorines with samples that measured below the LOQ (*14*), we imputed values using the following calculation for each congener: [(1 – *p*) × LOQ], where *p* = proportion of samples < LOQ. This provides a more realistic mean missing value than using LOQ, 50% LOQ, or zero. Total PCBs were calculated as the sum of serum concentrations of those PCBs with fewer than 30% of values imputed (PCB congeners 105, 110, 118, 137, 138, 153, 170, 180, and 187). Similarly, we calculated the sum of DDT and its metabolites from *p,p′*-DDE, *o,p′*-DDT, and *p,p′*-DDT.

Data analysis. We examined univariate distributions of measured serum organochlorine concentrations. Linear regression was then conducted to examine trends in organochlorine concentrations by date of blood draw, mother's age, duration of pregnancy at blood draw, and pre-pregnancy BMI. Analysis of variance was performed to evaluate differences in organochlorine concentration by categorical variables—namely, race, place of birth, parity, occupation, and residence on farm. We examined each predictor separately in bivariate analyses with each organochlorine of interest as the outcome. Those organochlorines with greater than 30% imputed values (PCB congeners 101 and 156 and *o,p′*-DDE) were excluded from these analyses. Because of highly skewed organochlorine concentration distributions (long right-hand tails), we used log-transformed organochlorine concentration values. Thus, by exponentiating the beta coefficients, we obtained the percentage change in organochlorine concentration for a 1-unit change in the predictor variable.

Because we oversampled cognitive- and hearing-impaired children for this study, the current sample was not drawn purely at random. Therefore, weighted analyses that applied appropriate sampling weights and corrected for design effect were performed using the survey software in STATA version 6.0 (*20*). Due to their lipophilicity, organochlorine concentrations were strongly positively associated with total lipid levels. For this reason, we included in all predictive models (including those referred to as "bivariate") a term for total lipids. Predictive models were constructed using all variables associated with one or more of the organochlorines in the initial bivariate analyses. The final multiple linear regression models included terms for total lipids, age, race, BMI, date of blood draw, duration of pregnancy at blood draw, and occupational group. Because there is a strong association in this study between region of birth and race, the model with region of birth as a predictor did not include a term for race and vice versa. Information about farm residence was not available for 169 women in the study, so we evaluated this predictor in a separate model, which included all other terms from the final multivariate model.

Table 2. Characteristics of the current sample of women, Child Health and Development Study 1964–1967 (*n* = 399).

Characteristics	No.	Percent
Age (years)		
< 20	28	7.0
20–29	242	60.6
≥ 30	128	32.1
Unknown	1	0.3
Parity		
0	122	30.6
1–2	177	44.4
≥ 3	100	25.1
Race/ethnicity		
White	194	48.6
African American	165	41.4
Hispanic	7	1.8
Asian	20	5.0
Multiracial/other	13	3.3
Pre-pregnancy BMI (kg/m^2)		
< 19	37	9.3
19–24	284	71.2
25–29	53	13.3
≥ 30	19	4.8
Unknown	6	1.5
Place of birth		
Southeastern United States	145	36.3
California	145	36.3
Other states[a]	82	20.6
Outside United States	26	6.5
Unknown	1	0.3
Occupation		
Housewife	222	55.6
Factory/household	35	8.8
Secretary/clerical	112	28.1
Professional	29	7.3
Unknown	1	0.3
Farm residence[b]		
Yes	48	12.0
No	182	45.6
Unknown	169	42.4

[a]States other than the southeastern states or California. [b]Residence on a farm > 5 years before the age of 15.

Results

Characteristics of our sample are presented in Table 2. Of the 399 women in our sample, one-third were ≥ 30 years of age. For 31% of the women, this was their first live birth; 25% had three or more previous births. Forty-nine percent of the women identified themselves as white, and 41% as black; the remaining 10% were Hispanic, Asian, or other. Race and region of birth were strongly associated: Of the 145 women born in the Southeast, 93% were nonwhite, and of nonwhites, 70% were born in the Southeast (data

not shown). More than one-half of the sample identified their occupation as housewife (56%), more than 25% worked in secretarial or clerical jobs, with the remainder split between blue collar and professional occupations. Twelve percent lived on a farm for more than 5 years during their childhood.

Distributions of each PCB congener and pesticide are shown in Table 3. The most abundant PCB congener was PCB 153, followed by 138, 118, and 180. Mean concentration of *p,p′*-DDT was more than seven times that of *o,p′*-DDT; mean concentration of *p,p′*-DDE was about four times that of *p,p′*-DDT.

Bivariate analyses revealed significant associations for some but not all of the measured organochlorines with the following examined predictors: date of blood draw, age, race, BMI, place of birth, occupation group, and farm residence. Parity was the only variable not significantly associated with any of the organochlorines measured. The most notable results of the multivariate models are presented in Figures 1–4, which show percent change in organochlorine concentrations by influential predictors, controlling for total lipids, calendar date of blood draw, age, race, duration of pregnancy, pre-pregnancy BMI, and occupation. Bars on the figures represent 95% confidence intervals (CI) around the point estimate for percent change.

Date of blood draw. Figure 1 presents the percent change in serum organochlorine concentration per calendar year of blood draw. Serum concentrations of most individual congeners increased with advancing collection date of serum sample. For total PCBs the increase was 8% per year (95% CI, 1–16%). *p,p′*-DDE, *o,p′*-DDT, the sum of DDTs, and heptachlor epoxide showed small decreases with time.

Age. Figure 2 presents the percentage change in organochlorine concentrations per 5-year increase in maternal age. Many of the PCBs, particularly the more highly chlorinated congeners (153 with 6 chlorine atoms; 170, 180, 187, each with 7 chlorines), increased with age. No increase was observed for either of the DDTs, DDE, or heptachlor epoxide.

Race/ethnicity. Several organochlorines were higher in nonwhite as compared to white women (Figure 3). The differences were particularly evident for pesticides *p,p′*-DDT and *p,p′*-DDE, for which nonwhite (primarily black) women had concentrations that were, on average, 50% higher than those of white women. PCB congeners 180 and 187 and *o,p′*-DDT were also significantly elevated. Heptachlor epoxide concentrations did not differ by race.

Place of birth. Serum concentrations of DDT and its metabolites were higher among women born in the southeastern United States, as compared to the referents—namely, those born outside both California and the southeastern United States (data not shown). That is, after controlling for the other model covariates, women born in the Southeast had average *p,p′*-DDE concentrations that were greater by 56% (95% CI, 36–79%) than levels found in referent women; *o,p′*-DDT was greater by 31% (95% CI, 7–60%); *p,p′*-DDT by 52% (95% CI, 34–72%), and sum of DDTs by 55% (95% CI, 38–75%). Women born in California had 17% (95% CI, 3–32%) higher serum *p,p′*-DDT and 14% (95% CI, 1–30%) higher sum of DDTs than women born elsewhere in the United States outside of the Southeast. Differences in serum PCB concentrations by region of birth were not as consistent. Among women born in California, PCB 110 was 35% higher than among referent women, and PCB 187 was 13% lower than among those born in the southeastern United States. Heptachlor epoxide concentrations did not vary much by region of birth.

BMI. Figure 4 shows the percent change in serum organochlorine concentrations for each 5 kg/m^2 increase in BMI. Most of the individual organochlorines, primarily the PCB congeners and *p,p′*-DDE, as well as total DDTs and metabolites, decreased with increasing BMI. For total PCBs the decline was 11% (95% CI, 6–16%) per 5-unit increase in BMI, and for the sum of DDT and metabolites, it was 8% (95% CI, 1–14%). Heptachlor epoxide, however, rose with increasing BMI, 9% (95% CI, 2–16%), as did *o,p′*-DDT and *p,p′*-DDT.

Occupation. Compared to housewives, pre-pregnancy occupation outside of the home did not show a consistent relationship with serum organochlorine concentrations (data not shown). Factory and household workers had lower serum concentrations of both PCB 137 (27%) and heptachlor epoxide (14%). Professionals, however, had higher levels of *p,p′*-DDE (33%), sum of DDTs (29%), and heptachlor epoxide (24%). In secretarial and clerical workers, average PCB 137 was 18% lower, while average *p,p′*-DDT was 10% higher .

Residence on a farm. Compared to women who had lived ≤ 5 years on a farm before the age of 15, women who had lived on a farm for more than 5 years in their

Table 3. Serum organochlorines measured in the current sample of women, Child Health and Development Study 1964–1967 (*n* = 399).

Organochlorine compound	No. imputed values (%)	Wet-weight basis (ppt)			Per-lipid basis (ng/g lipid)		
		Mean ± SD	Median	10th–90th percentiles	Mean ± SD	Median	10th–90th percentiles
PCB congeners							
101	245 (61.4)	252 ± 302	92	92–553	32 ± 39	15	10–67
105	33 (8.3)	550 ± 448	426	200–1,046	71 ± 58	55	26–138
110	87 (21.8)	477 ± 810	191	78–1,188	63 ± 110	24	10–158
118	1 (0.3)	674 ± 366	608	354–1,074	86 ± 47	76	45–132
137	103 (25.8)	484 ± 621	255	100–1,178	64 ± 85	32	11–160
138	5 (1.3)	945 ± 472	844	516–1,550	120 ± 60	107	68–188
153	2 (0.5)	1,161 ± 515	1,057	648–1,856	148 ± 67	133	84–239
156	182 (45.6)	236 ± 199	196	101–437	31 ± 29	21	11–61
170	2 (0.5)	267 ± 159	227	127–441	34 ± 20	30	16–56
180	1 (0.3)	601 ± 319	529	308–912	76 ± 38	69	40–114
187	8 (2.0)	263 ± 163	226	116–446	33 ± 19	29	15–58
Total PCBs[a]	—	5,423 ± 2,310	4,747	3,105–8,678	696 ± 308	616	378–1,115
Pesticides							
o,p′-DDE	191 (47.9)	326 ± 587	121	58–777	43 ± 83	15	6–99
p,p′-DDE	1 (0.3)	53,888 ± 35,302	45,308	21,114–96,377	6,854 ± 4,804	5,878	2,720–11,501
o,p′-DDT	8 (2.0)	2,056 ± 1,566	1,593	645–3,885	268 ± 217	201	82–523
p,p′-DDT	0 (0.0)	14,984 ± 8,828	12,413	6,480–27,044	1,931 ± 1,247	1,611	855–3,512
Total DDT[b]	—	70,928 ± 40,931	61,369	31,172–122,506	9,052 ± 5,595	7,951	4,149 –15,102
Heptachlor epoxide	60 (15.0)	613 ± 618	426	191–1,157	79 ± 89	54	28–151

[a]Sum of all congeners with < 30% imputed values. [b]Sum of DDT and DDE metabolites with < 30% imputed values.

youth had 13% (95% CI, 1–24%) lower serum concentrations of total PCBs, as well as lower concentrations of PCBs 110, 137, and 170; *o,p′*-DDT was lower by 28% (95% CI, 10–42%), and *p,p′*-DDT by 16% (95% CI, 1–28%) (data not shown).

Discussion

As expected, the women from the CHDS cohort had higher mean serum organochlorine levels than has generally been found in more recent general population samples in North America (*21–25*). Of the other congener-specific analyses of serum PCB concentration we identified, the only North American groups with higher published levels than our CHDS sample were an Inuit population (*21*), who consume large quantities of contaminated marine mammals, and groups in Wisconsin (*26*) and Michigan (*22*) with high consumption of Great Lakes fish. Other groups with higher levels included Yucheng women 14 years after the accidental contamination of rice oil (*27*) and occupationally exposed individuals in Finland (*28*). The *p,p′*-DDE levels in the CHDS sample are about twice as high as were observed by Longnecker and colleagues (*29*) in serum samples from pregnant women enrolled in the Collaborative Perinatal Project (CPP) between 1959 and 1965; however, summed PCB levels in the CHDS sample are comparable to those observed in the CPP sample. Serum heptachlor epoxide concentrations in our CHDS sample are similar to serum levels measured in rural U.S. residents during the late 1980s (*30*); about two times the levels reported from a study of an elderly population in Germany in the early 1980s (*31*); about four times the level in 20- to 60-year-old adults exposed to contaminated milk in Hawaii in the early 1980s (*32*); but substantially below the level reported in a large population-based U.S. sample of 45- to 74-year-olds from the late 1970s (*33*).

PCBs and the pesticides DDT and heptachlor were still in widespread use when the CHDS drew blood samples from women in this study. Possible exposure pathways might have included personal contact with everyday products containing PCBs, application of pesticides in or near their homes or to nearby agricultural areas, and ingestion of produce treated with pesticides, as well as through bioaccumulation pathways we currently consider most important (e.g., fish, dairy, and meat consumption). Thus, body burdens reflect both recent and past exposures in this population, whereas in more recent studies, past exposures (or high ingestion of foods that have accumulated past exposures) will dominate. Compared to more recent population studies, the lower chlorinated, shorter half-life PCB congeners (e.g., 101, 105, 110, and 118) constitute a greater proportion of the total, whereas the higher chlorinated, longer half-life congeners (e.g., 180 and 187) constitute a smaller proportion of the total (*22,34–38*). This pattern reflects the CHDS population's contemporaneous PCB exposure, as the congeners with shorter half-lives are in greater proportion than is seen in recent population studies. The most abundant PCB congener measured in the CHDS sample was PCB 153, followed by 138, 118, and 180, in that order. These patterns are consistent with exposures to both Aroclors 1254 and 1260, since both contained relatively high concentrations of PCB 153 and 138; Aroclor 1254 had high concentrations of PCB 118; and Aroclor 1260 had high concentrations of PCB 180 (*39*). Concentration of *p,p′*-DDT in the CHDS sample is much higher than has been found in more recent population studies (*40–42*). In recent population studies, *o,p′*-DDT is not detected in most samples (*38,42*), whereas in the CHDS cohort, < 10% of measures were below the LOQ. Median *p,p′*-DDE serum concentration in the CHDS sample is about four times as high as *p,p′*-DDT, a ratio generally consistent with more recent exposure to the parent compound (DDT), since DDT's half-life is substantially shorter than DDEs. An increasing DDE:DDT ratio after DDT was banned is evident in studies of populations over time (*40,41,43*).

A number of studies have consistently found higher body burdens of organochlorines with increasing age (*24,25,44–46*). In our study, we found an increasing trend with age for serum levels of PCBs, but not the DDTs, DDE, or heptachlor epoxide. Older women have been exposed to organochlorines for a longer period and would therefore be expected to have accumulated a higher body burden. The positive association between age and organochlorines is partially attributed to a "cohort effect" (*24*) because older women in current populations are more likely than younger women to have lived during a period of peak exposure. In this study, current PCB exposure for these women is likely the highest during their lifetime, since the study period corresponds to an era of increasing and nearly peak production and use. Our finding of no significant association between age and DDT, DDE, or heptachlor epoxide levels is inconsistent with other studies (*24,25,44,47*). One explanation is that past exposures of these women may have been higher than concurrent (1960s) environmental levels, so that the amount excreted is roughly comparable to the amount being

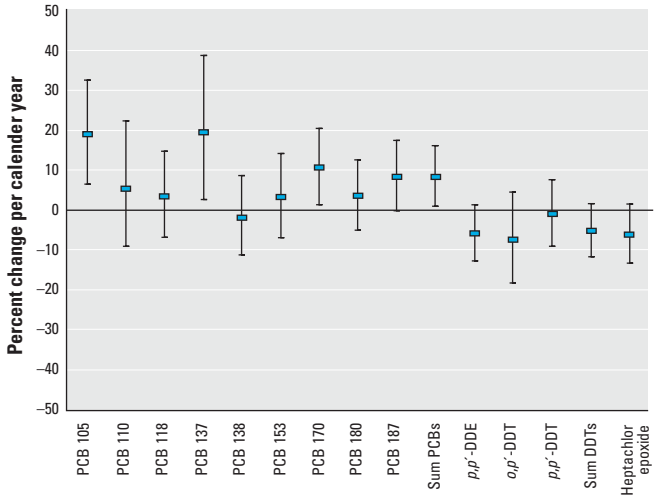

Figure 1. Percent change in serum organochlorine level per calendar year of blood draw, controlling for total lipids, age, race, BMI, occupation, and duration of pregnancy at blood draw. Error bars indicate 95% CI.

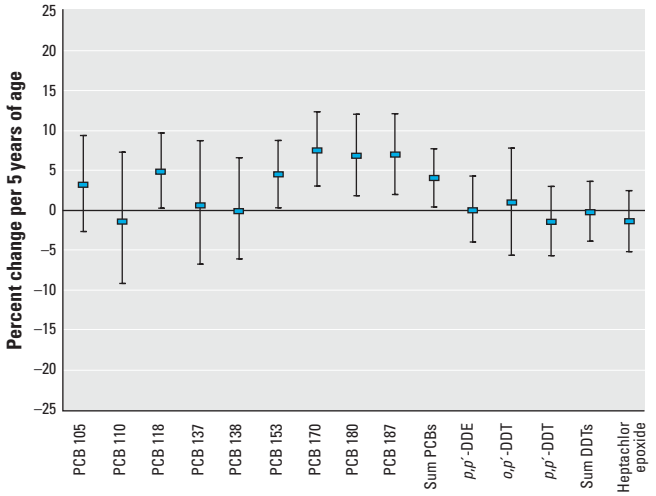

Figure 2. Percent change in serum organochlorine level per 5-year increase in age, controlling for total lipids, race, BMI, occupation, duration of pregnancy at blood draw, and calendar year of blood draw. Error bars indicate 95% CI.

absorbed from the urban/suburban environment where the women lived.

In our study, some PCB congener concentrations (105, 137, 170, 187), as well as total PCBs, increase with calendar time (i.e., from late 1963 to April 1967). This finding likely reflects the increased production and use of PCBs during this period. Until 1957, PCBs were widely used in "closed system" applications (e.g., in electrical transformers and capacitors). After 1957 and throughout the 1960s, though closed system applications still predominated, use in other products (such as in hydraulic fluids, polyvinyl chloride, flame retardants, paints, wood preservatives, carbonless copy paper, and textiles) became widespread and eventually amounted to about 40% of total PCB usage in the United States (*48,49*). As one example, annual carbonless copy paper production volume by the NCR Corporation increased steadily over this period, from about 10,000 tons in 1957 to > 90,000 tons by 1970 (*50*). Environmental releases of Aroclor 1242, 1248, 1254, and 1260 increased during the 1960s, and it has been estimated that the release of Aroclor 1260 peaked in 1964 (*51*). Increasing PCB concentrations in human population studies from this time period mirror this trend (*52*).

We did not find an association between calendar time and DDE and DDT concentrations in the CHDS sample, perhaps because these compounds were not being used in urban and suburban areas around the San Francisco Bay Area at that time. The U.S. Environmental Protection Agency's (EPA's) general population survey of adipose tissue observed a steady decline of total DDT levels after the early 1970s (*47,53*). Few data are available from the 1960s, but the decline in California may have been underway during the period of our study. Heptachlor epoxide levels measured in the general U.S. population remained relatively constant throughout the 1970s and into the 1980s (*47,53*); our findings showed no appreciable change in heptachlor epoxide levels during the mid-1960s.

Both nonwhite race and region of birth were important predictors of some serum organochlorine concentrations, particularly DDT and its metabolites. Nonwhite, primarily black, women's *p,p′*-DDE and *p,p′*-DDT concentrations were about 50% higher than white women's, and significantly high concentrations for nonwhites were also observed for *o,p′*-DDT and PCBs 180 and 187. Other studies have reported racial differences in measured organochlorines (*24,54*). In the U.S. EPA human monitoring program, blacks had adipose DDE levels 70% higher than did whites (*54*). In the second National Health and Nutrition Examination Survey (NHANES II) 1976–1980 population, nonwhites had higher serum *p,p′*-DDE compared to whites (*24*). Similar to our findings, heptachlor epoxide did not vary by race in the NHANES II population (*24*).

Our regional comparisons used as the referent all areas outside California and the Southeast. Women born in the Southeast had significantly higher *o,p′*-DDT, *p,p′*-DDE, *p,p′*-DDT, and sum of DDTs, and those born in California had higher serum *p,p′*-DDT and sum of DDTs. Similar to our findings, NHANES II found higher serum *p,p′*-DDE in those from the South or West, compared to the Northeast or Midwest, and in the U.S. EPA human monitoring program, adipose DDE levels were higher in the Southeast and California than elsewhere in the United States (*54*). We also found regional differences for PCB congeners 110, 137, and 187. In particular, PCB 110, which was present in high concentrations in Aroclor 1254 (*39*), was higher in those born in California, whereas PCB 187, which was present almost exclusively in Aroclor 1260 (*39*), was highest in those born in the Southeast. A 1989–1990 sample from the Nurses' Health Study showed higher PCB levels in women from the Northeast or Midwest compared to those from the South or West (*25*), but no congener-specific data were reported. Although we did not observe any regional differences for heptachlor epoxide, in NHANES II concentrations were higher in the South and West compared to the Midwest or Northeast (*24*).

Geographic comparisons for the current study have been based on place of birth, not current residence, while the above studies relied on residence at the time a biological sample was taken (*24,25,54*); this may explain differences when comparing our results. Birthplace addresses a possible cause of observed racial differences in organochlorine levels. If, like most of the white women, all of the nonwhite women in the CHDS sample had lived only in California, it would be reasonable to hypothesize that differences in lifestyle (diet choices, for example), occupational exposures, and even metabolism may explain higher organochlorine levels in nonwhites. In this sample, however, 70% of nonwhites were born in the Southeast. Migration of blacks during the 1940s and 1950s led to a 10-fold increase in the black population in the study area between the 1940 and 1960 censuses (*55,56*). Therefore, many of the women in our study likely spent a significant part of their youth outside of California.

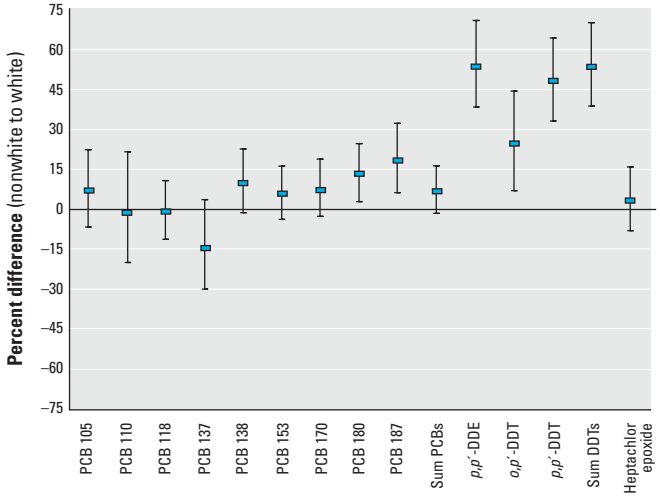

Figure 3. Percent difference in serum organochlorine level comparing nonwhite to white women, controlling for total lipids, age, BMI, occupation, duration of pregnancy at blood draw, and calendar year of blood draw. Error bars indicate 95% CI.

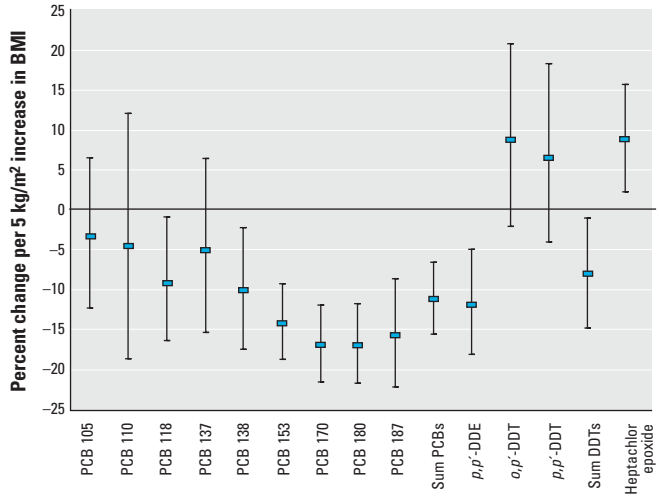

Figure 4. Percent change in serum organochlorine level per 5 kg/m^2 increase in BMI, controlling for total lipids, age, race, occupation, duration of pregnancy at blood draw, and calendar year of blood draw. Error bars indicate 95% CI.

Because the measured organochlorines, especially the PCBs, may persist for decades (*4,9*), region of birth may partially explain racial differences observed in this study. Because of the strong association between race and place of birth in this sample, we are unable to tease these two variables apart.

In contrast to several published studies (*35,45,57*), we did not find parity to be an important predictor of organochlorine body burden. In other subsets of the CHDS cohort, about 35% of women attempted breast-feeding, and relatively few breast-fed for 3 months or more (*58*). Because transfer of organochlorines during gestation is much lower than via breast-feeding, the effect of parity on women's body burden would be small in the absence of extended breast-feeding.

We found inverse associations between BMI and concentrations of all measured organochlorines except *o,p′*-DDT, *p,p′*-DDT, and heptachlor epoxide. A mid-1990s study of breast milk in Germany (*59*) similarly found a negative relationship of BMI with lipid-adjusted PCBs but not with pesticides. However, a study of residents near a factory that had produced PCBs and DDT in the past found a positive association with PCBs and pesticides after adjustment for weight loss but not lipids (*60*). A study of Great Lakes fish consumers also observed a positive association between total coplanar lipid-adjusted PCB levels and BMI (*61*). Other studies have observed no association with PCBs using different criteria for this judgment (*31,62*); both of these studies found associations with one or another pesticide, but not the same pesticides. BMI provides a crude measure of body adiposity. Because organochlorines are stored in fatty tissues, those with higher body adiposity may have the same (or even greater) absolute body burden of organochlorines, but dilution due to larger volume of tissue or fluid would occur. This would tend to explain a negative association. However, if those with higher adiposity have consumed more foods contaminated with organochlorines, a positive association might be expected. Lipid metabolism rates may also differ for those with greater body mass, and studies differ in whether and how they adjust for lipids. The relationship would also likely be influenced by the rate of absorption, such that those who are concurrently being exposed might express different relationships from those for whom excretion rates far exceed absorption. Different relationships would be expected for parent compounds versus metabolites, as a function of the rates of metabolism and differential rates of excretion. These complexities may explain the lack of consistency in the cross-sectional associations between BMI and organochlorine concentrations. In our population, PCB exposure was not only ongoing but may have been increasing; current DDT exposure in these women may have been low relative to their prior exposures, particularly for those who migrated from the southeastern United States.

Because DDT and heptachlor were widely used in agricultural applications, we expected women who had resided on farms to have higher body burdens of these pesticides. Serum *p,p′*-DDE, *p,p′*-DDT, and heptachlor epoxide were higher among farm residents in the NHANES II sample (*24*); and higher *p,p′*-DDT levels in breast milk were found in Mexico City residents (1994–1995) who had lived in agricultural areas (*45*). Surprisingly, just the opposite relation was observed for serum DDT concentrations: women who had lived more than 5 years on a farm had significantly lower serum *o,p′*-DDT and *p,p′*-DDT levels than those who had spent ≤ 5 years on a farm. The explanation for these findings is unclear. It is possible that exposures to DDT were lower for those living on farms because of its widespread use in populated areas, especially for mosquito control in the Southeast. Several PCB congeners were also lower in those with childhood farm residence. If these women had spent relatively more time in rural areas, lower PCB concentrations might be expected because these compounds are generally higher in urban or industrial areas (*3,63*). Serum PCB concentrations did not differ consistently by the occupational groupings we were able to compare in this cohort.

Because organochlorines concentrate in lipids, variation in serum concentrations will result from variability in serum lipids. Blood samples in the CHDS were nonfasting, which can lead to as much as a 30% increase in measured organochlorines, simply due to elevations in blood lipids after a fatty meal (*18*). Often organochlorine concentrations are divided by total lipids for each sample, which allows appropriate cross-study comparisons of organochlorine burdens in different populations. In this study, a number of our predictors of interest are also related to blood lipid levels. Lipids, and particularly triglycerides, increase substantially during the second and third trimesters of pregnancy (*64,65*); African-American women have been found to have lower blood triglycerides than white women (*66*); increasing age has also been positively associated with blood lipids (*67*). We therefore chose to examine predictors of serum organochlorines with total lipids as a separate model term and serum organochlorine concentration as the dependent variable. This approach reduces the likelihood of bias due to lipid–covariate relationships that are independent of serum organochlorine concentration.

Finally, we note that measurement error may explain why some organochlorines but not others displayed associations with specific predictors. The relative error was greater for those organochlorines present at lower concentrations, including PCBs 105, 110, and 137, as well as *o,p′*-DDE.

Conclusion

In this study, we report the predictors of serum levels of 11 individual PCB congeners, total PCBs, *p,p′*-DDE, *o,p′*-DDT, *p,p′*-DDT, and their sum, and heptachlor epoxide in a cohort of pregnant women from the 1960s. As compared with today's populations in western countries, the organochlorine levels are high, as they reflect recent and ongoing exposure. PCB serum concentrations increased with advancing calendar date at blood draw during the period 1963–1967, probably due to greater production and use during this time period, including in consumer products. We found that serum concentrations of several individual PCB congeners, particularly highly chlorinated ones, as well as the sum of PCBs, increased with age. Nonwhite women had higher concentrations of DDT and its metabolites, as well as of the higher chlorination PCBs. Among those born in the southeastern United States or in California, we also observed higher concentrations of DDE, DDT, and some of the higher chlorinated PCBs. It was not possible to determine independent effects from place of birth and race; it is possible that the race difference was primarily due to most African Americans having been born and spending some part of their lives in the Southeast, where DDT was more heavily used. Most of the PCB congeners, as well as *p,p′*-DDE, decreased with increasing BMI. Heptachlor epoxide, however, showed a positive association with BMI.

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