The Effects of PCB Exposure and Fish Consumption on Endogenous Hormones

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Previous studies have suggested that exposure to polychlorinated biphenyls (PCBs) may alter thyroid function, but data on effects of PCB exposure on other endogenous hormones has been lacking. The current study is ancillary to a larger investigation of the effects of Great Lakes fish consumption on PCBs and reproductive function. In the current study we examine associations of PCBs, 1,1-bis (4-chlorophenyl)-2,2-dichloroethene (DDE), and fish consumption with thyroid and steroid hormones in 178 men and PCBs, DDE, and fish consumption with thyroid hormones in 51 women from the original study. Serum PCB level and consumption of Great Lakes fish are associated with significantly lower levels of thyroxine (T_4) and free thyroxine index (FTI) in women and with significantly lower levels of T_4 in men. Fish consumption, but not PCB level, is significantly and inversely associated with triiodothyronine (T_3) in men. Results for thyroid-stimulating hormone (TSH) are inconsistent. Among men, there are significant inverse associations of both PCB and fish consumption with sex hormone-binding globulin (SHBG)-bound testosterone, but no association with SHBG or free testosterone. There are no significant overall associations of PCB, DDE, or fish consumption with estrone sulfate, follicle-stimulating hormone, luteinizing hormone, or dehydroepiandrosterone sulfate. The results of this study are consistent with previous studies showing effects of fish consumption and PCB exposure on thyroid hormones and suggest that PCBs may also decrease steroid binding to SHBG. Elucidation of specific mechanisms must await future investigations. *Key words*: consumption, fish, hormones, PCBs, steroid, thyroid. *Environ Health Perspect* 109:1275–1283 (2001). [Online 30 November 2001] *http://ehpnet1.niehs.nih.gov/docs/2001/109p1275-1283persky/abstract.html*

There is an increasing body of animal data suggesting that high levels of polychlorinated biphenyl (PCB) exposure may be associated with a wide variety of health effects, including changes in hormonal balance. Of particular interest are effects on thyroid hormones. The concern over *in utero* effects of low-level PCB exposure relates to known neurotoxic effects of hypothyroidism on developing organisms (*1*), with potential effects being delayed neurodevelopment, decreased intelligence, and hearing deficits. Human studies of low-level exposures, however, are sparse. Alterations in thyroid hormones have been seen after exposure to PCBs and polychlorinated dibenzofurans after a mass contamination in Yusho, Japan (*2*), in children living near an industrial waste incinerator in Germany (*3*), and in some (*4,5*) but not all studies (*6*) of children exposed to low levels of PCBs *in utero*. Studies of PCB effects on other hormones have been notably lacking.

A consortium that was formed to assess exposure risks of contaminated Great Lakes fish consumption (*7,8*) offered a unique opportunity to examine the effects of low-level PCB exposure and fish consumption on endogenous hormone levels. This consortium is an outgrowth of The Great Lakes Water Quality Agreement of 1978 in which the health departments of Wisconsin, Illinois, Indiana, Ohio, and Michigan formed the consortium to assess health risks of exposure to contaminated Great Lakes fish (*9*). Previous investigations of this cohort have shown that PCB and DDE levels were significantly correlated with age, body mass index, male versus female sex, and frequency of sport fish and Great Lakes sport fish consumption (*10,11*). In this report we summarize the associations of thyroid hormones with PCB and DDE levels in males and females, and the associations of steroid hormones with PCB and DDE levels in males in a subset of the original cohort.

Methods

Prior to initiation of this study protocol, it was reviewed and approved by the University of Wisconsin-Madison Medical School Human Subjects Committee and University of Illinois-Chicago Human Subjects Review Boards.

Original Study

Sample selection. Inventory was taken of left-over serum donated from charter boat captains, Wisconsin anglers, and unexposed referent participants in the Consortium for the Health Assessment of Great Lakes Sport Fish Consumption full study. A detailed description of the full study protocol has been previously published (*7*). Briefly, men and women who had obtained a license to conduct charter boat services on Lakes Michigan, Huron, and Erie and a sample of Wisconsin anglers were administered a telephone survey in fall 1993. If the participant had had a child since 1970, his spouse was interviewed. Approximately 1,800 charter boat captain households and 129 Wisconsin angler households completed the survey, and 532 participants donated a blood sample for chemical analysis. Referent participants who reported eating less than six meals of Great Lakes sport fish in each year for the last 20 years were administered the same telephone survey in 1994. These referent participants were chosen through random digit dialing and frequency matched by the first six telephone digits to the charter boat captain sample by geographic region. Over 1,200 households completed the survey and 100 participants donated a blood sample.

Fish consumption survey. In 1993, information about fish consumption habits and demographics were obtained from a telephone survey administered by the University of Wisconsin-Extension Survey Research Laboratory, Madison, Wisconsin (WSRL). Information about the number of total fish meals consumed in the last 12 months was obtained using the following open-ended

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We thank M. Wolff for her insightful comments, J. Piorkowski for her help coordinating the hormone assays, and D. Hryhorczuk for his help in establishing the collaboration.

This research was funded by the Agency for Toxic Substances and Disease Registry, Atlanta, Georgia (grant no. H75/ATH598322).

Received 13 February 2001; accepted 11 May 2001.

question: "About how many meals of fish did you eat per week or per month in the last 12 months, including all types of freshwater and saltwater fish, whether fresh, canned, smoked, or frozen?" Each participant was asked if he had eaten Great Lakes (GL) sport fish in the last year; if he had, the participant was asked how many meals of different types of GL sport fish he consumed in that time period. The types of GL sport fish meal categories were lake trout; brown trout; rainbow trout, chinook, or coho salmon; carp or catfish; and perch, smelt, or walleye. Information about the number of years they consumed sport fish and GL sport fish was also obtained. Demographic information obtained included date of birth, height, and weight. In 1994, total fish meals and demographics were collected from referent subjects using the same survey techniques. After completion of each telephone survey, a sample of the respondents were invited to donate blood for chemical analysis. Selection criteria for blood collection recruitment has been previously published (*10*).

Blood collection. The protocol used by all research staff for specimen collection, preparation, and shipment was prepared by the Centers for Disease Control and Prevention, Atlanta, Georgia. Prior to donating blood, each subject gave informed consent. Approximately 30 mL of serum was collected for PCB and DDE analysis. Details of the blood collection protocol have been published (*10*).

Overview of Hormone Study

Eligibility. To be eligible for recruitment in the hormone study, the participant had a known PCB/DDE level from the prior study and a minimum leftover sample volume of 3.5 mL. Serum samples donated from female participants ≤ 40 years of age were eliminated because of limited funds and a lack of information about their menstrual cycle at the time of the blood collection. A register of 438 persons met the criteria and were invited to participate.

Initial recruitment for the hormone study. Potential participants were sent the following materials: *a*) a recruitment letter inviting them to participate in the study; *b*) a consent form describing the study and asking permission to analyze leftover serum for hormone levels; and *c*) a five-question screener questionnaire obtaining information about endocrine disorders, medication taken at time of blood draw that might affect hormone levels, and menopausal status. Three hundred nine signed consent forms and questionnaires were returned for a response rate of 71%.

Hormone study telephone survey. In 1997, all potentially eligible persons (determined after review of the five-question screener) were administered a survey by the WSRL. The survey was developed by staff from the University of Illinois-Chicago and University of Wisconsin-Madison and contains four modules: male module; female module; male couple module; and female couple module. All modules collected information regarding medical history, demographics, medication use, lifestyle habits, and information about the cohort's children. The male module obtained information about medical conditions, including impotence, low sperm count, and prostate cancer. Specific information obtained from the female module included menstrual and pregnancy history, usage of contraceptives, and medical conditions including breast cancer and uterine cancer. Participants who were part of a couple were administered the male or female couple module. Trained interviewers from WSRL administered the survey to each person. Two hundred forty-two persons completed the survey.

Exclusion criteria. A total of 79 people (both male and female) were excluded from the study, 54 after the responses to the five-question screener questionnaire were reviewed and 25 after the telephone survey responses (survey described below) were reviewed. Reasons for exclusion included history of thyroid disease (n = 20), diabetes (n = 16), thyroid disease and diabetes (n = 1), other endocrine problem (n = 4), prednisone therapy (n = 2), oral contraceptives or hormone replacement therapy (n = 17), or missing data (n = 19). The final study group included 179 males and 51 females. Of these, 117 males and 38 females were captains, 34 males and 4 females were anglers, and 28 males and 9 females were included in the comparison referent group.

Laboratory Analyses

PCB and DDE analyses. All samples were analyzed for DDE and 89 PCB congeners at the Wisconsin State Laboratory of Hygiene (Madison, WI) and the Michigan Department of Community Health (Lansing, MI). The PCB congeners were represented by 62 peaks using capillary column gas chromatography with electron capture detection (*12*). A detailed description of the PCB and DDE laboratory protocol has been published elsewhere (*10*). Measurements were made from a subsample of specimens for 8 polychlorinated dibenzo-*p*-dioxins, 10 polychlorinated dibenzofurans, and 4 coplanar PCB congeners according to the high-resolution mass spectrometric method of Patterson et al. (*13*). We summarized the results on a lipid-adjusted (parts per trillion) × toxic equivalent factor (TEF) basis, as described by Akins et al. (*14*). Copies of a summary of the methods, quality control protocols, and limits of detection are available upon request from the authors.

Censored data. Researchers have described several methods to summarize data in which a nondetectable code is assigned the result for a specific congener (*15*). The nondetectable values for the all PCB congeners were imputed by using the following guidelines: If < 50% of the sample had nondetectable values for a congener, the concentration for the nondetectable was imputed by dividing the limit of detection by the square root of 2. If > 50% of the sample had nondetectable values for a congener, the concentration was assigned half the limit of detection. Next, each imputed concentration value was compared to the sample median for the specific congener. If it was greater than the median, the median was assigned as the final concentration. If it was less than the median, the imputed value was assigned. Total PCB is the sum of the concentration of all congeners tested.

Serum lipids, dioxins, and furans were available for 76 participants. For these participants lipid-adjusted total PCB (parts per billion) was calculated from the formula:

$$\text{Lipid-adjusted total PCB in ppb} = (\text{Total PCB in ppt/total lipid in mg/dl}) \times 102.6.$$

Hormone Analysis

Quality assurance/quality control procedures. Samples from 16 males and 13 females with excess serum, selected from the 255 samples, were split for quality assurance/quality control (QA/QC) studies. The 255 serum samples along with the 29 QA/QC samples were sent to Northwestern Medical School Laboratory (Chicago, IL). Staff at Northwestern further split all samples and forwarded the replicates to Smith Kline Laboratories (Chicago, IL) for analyses of thyroid hormones. Serum specimens were analyzed by technicians who were unaware of the participants' exposure group.

Thyroid hormones. Thyroid hormone analyses on male and female sera samples were performed by SmithKline Beecham Clinical Laboratories (Van Nuys, CA). Ultrasensitive thyroid-stimulating hormone (TSH), total triiodothyronine (T_3), thyroxine (T_4), T_3 uptake, and free T_4 index (FTI) were analyzed at the facility. Some sera samples from males did not have sufficient volume for all analyses: 3 for TSH, 16 for T_3, and 13 each for T_4, FTI, and T_3 uptake. Quality control studies yielded the following coefficients of variation (CVs) for the indicated number of split samples: TSH = 10.4%, n = 26; T_3 = 5.4%, n = 13; T_3 uptake = 3.0%, n = 16; T_4 = 7.4%, n = 16; and FTI = 8.7%, n = 16.

Thyroxine and free thyroxine index. T_4 was determined through an immunoassay in which the control was combined with an

enzyme-acceptor solution containing T_4 antibody, with a releasing agent, and enzyme-donor solution containing enzyme substrate. The reagents were mixed and incubated at 37°C, and the rate of hydrolysis was measured at 450 nm. The concentration of total T_4 in the patient specimens and controls were determined using a linear calibration curve (*16*). FTI was calculated from a T_3 uptake assay in which ^{125}I-labeled T_3 was used as the tracer in the T_3 uptake assay to fill the unbound thyroxine-binding globulin (TBG) sites. The remaining tracer was bound by albumin covalently immobilized to para-magnetic particles. Separation of bound from unbound tracer was by magnetic separation and decantation of the supernatant. The amount of T_3 radioactivity bound to the immobilized albumin binder varies inversely with the level of unbound TBG in the sample.

Total T_3. T_3 was determined by Ciba-Corning ACS Chemiluminometric Assay (Ciba-Corning, Medfield, MA) (*17–19*). The Chiron Diagnostics ACS:180 T_3 assay (Chiron Diagnostics, Emeryville, CA) is a competitive immunoassay using direct chemiluminescent technology. T_3 in the patient sample competes with a T_3 analog, which is covalently coupled to paramagnetic particles in the solid phase for a limited amount of acridinium ester-labeled monoclonal mouse anti-T_3 antibody in the Lite Reagent (Ciba-Corning). An inverse relationship exists between the amount of T_3 present in the patient sample and the amount of relative light units detected by the system.

TSH. TSH was measured by an Immulite (Diagnostics Products Corporation, Los Angeles, CA) third generation method, which is a solid-phase, two-site chemiluminescent immunometric assay. The solid phase, a polystyrene bead enclosed within an immulite test unit, was coated with a monoclonal antibody specific for TSH. While the participant serum sample and alkaline phosphatase-conjugated polyclonal antibody were incubated for approximately 60 min at 37°C with intermittent agitation, TSH in the sample was bound to an antibody sandwich complex. After unbound conjugate was removed by a centrifugal wash, substrate was added, and the test was incubated for another 10 min and then read by chemiluminescence.

Steroid hormones. Steroid hormone analyses were performed on serum from males in the cohort by the Immunoassay Core Facility Laboratory of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Sex hormone-binding globulin. We used the Delphia system for the assay of sex hormone-binding globulin (SHBG) in serum; materials were obtained from Wallac, Inc. (Gaithersburg, MD). This solid phase, two-site, time-resolved fluoroimmunometric assay uses a sandwich technique. The intraassay and interassay CVs in recent assays have been 6% and 8%, respectively (*20*).

Dehydroepiandrosterone sulfate. We measured dehydroepiandrosterone sulfate (DHEAS) in unextracted serum by radioimmunoassay as described previously (*21*). Tritiated tracers were obtained from Nuclear Corp. (Boston, MA). Antiserum was obtained from ICN Biochemcicals, Inc. (Costa Mesa, CA; cross-reactions: 36% androsterone, 12% 5-androstane-3,17-dione, 3% androst-4-ene-3,17-dione). Antibody-bound ligand was separated from unbound ligand by the addition of dextran-coated charcoal. The intraassay and interassay CVs in recent assays were 4.6% and 10.9%, respectively.

Follicle-stimulating hormone. Antiserum and standards were obtained from the National Hormone and Pituitary Program of the NIH at Georgetown University Medical Center. Iodinated follicle-stimulating hormone (FSH) was obtained from Incstar Corp. (Stillwater, MN). This double antibody method for measuring FSH in serum has been described previously (*22,23*). The intraassay and interassay CVs in our recent assays were 2.55 and 3.5%, respectively.

Luteinizing hormone. We measured luteinizing hormone (LH) by a coated tube radioimmunoassay. Materials were obtained from Diagnostics Products Corporation. In this assay, LH is captured between monoclonal anti-LH antibodies immobilized on the inside surface of the polystyrene tube and the ^{125}I-labeled polyclonal anti-LH tracer. Results are expressed in milli-International Units per milliliter in terms of the World Health Organization's First International Reference preparation of LH for immunoassay (IRP). The sensitivity is approximately 0.15 mIU/mL. Intraassay and interassay CVs average 3.0 and 7.1%, respectively.

Testosterone. We measured testosterone in serum using a coated tube assay obtained from Diagnostic Systems Laboratories. This assay uses ^{125}I-testosterone as the tracer. The antiserum cross-reacts < 0.9% with androstenedione and androstenediol, and 5.8% with dihydrotestosterone. Intraassay and interassay CVs in our recent assays were 4.9% and 7.5%, respectively.

SHBG-bound testosterone. SHBG-bound testosterone was determined as described by Bonfrer et al. (*24*) A 0.2 mL volume of serum diluted 1/8 with buffer was equilibrated with ^{3}H-estradiol overnight at 40°C. A 0.10 mL suspension of a conconavalin-A Sepharose conjugate (Amersham/Pharmacia, Piscataway, NJ) was added to the serum. SHBG bound to the conconavalin-A during a 30 min incubation period at room temperature. Testosterone in the serum maintained its equilibrium concentration with SHBG in the presence of endogenous factors such as other androgens, estrogens, and free fatty acids (*24,25*). Separation of unbound ^{3}H-testosterone from that bound to the Sepharose conconavalin-A was achieved by centrifugation at 0°C to minimize dissociation of bound estradiol. A pool of human serum was used as an internal control. The intraassay and interassay CVs of our recent assays were 8.2 and 10.4%, respectively.

Free testosterone. The method of determining free testosterone depends on the equilibrium of ^{3}H-testosterone with testosterone in serum and separation of unbound ^{3}H-testosterone from ^{3}H-testosterone that is bound to SHBG and other serum proteins at 37°C. ^{3}H-Testosterone was purified by thin-layer chromatography within 1 week of use. We added 50 µL containing 40,000 counts per minute (cpm) ^{3}H-testosterone in methanol to 12 × 75 mm culture tubes, and the solvent was evaporated. Subsequent procedures were performed in a 37°C room. A 0.3 mL aliquot of serum to be analyzed was added to the tubes containing the tracer and equilibrated for 30 min. An aliquot of 25 µL was taken from the equilibrated solution for counting and the remainder was added to centrifugal filters that had a molecular weight cut-off of 10,000 (Ultrafree-MC Centrifugal Filter Units; Millipore, Bedford, MA). The separation was accomplished by centrifugation for 2 min in a microcentrifuge at 12,000 × *g*. This provided 35–50 µL of filtrate; we used 25 µL for counting the unbound fraction. The percent free was the counts per minute in the filtrate/counts per minute in the serum before separation × 100. The CV of duplicates in our recent assays was 7.1%.

Estrone sulfate. In this assay we used a double antibody radioimmunoassay employing ^{125}I-estrone sulfate from Diagnostic Systems Laboratories. The antiserum is highly specific for estrone sulfate; among 25 steroids tested for cross-reactivity, only estrone (4.9%) estrone glucuronide (3.4%), estradiol 3-sulfate (1.0%), estradiol (0.3%), and estradiol glucuronide (0.1%) compete significantly for estrone sulfate. The intraassay CV was 6.0% from duplicate determinations, and the interassay CV was 6.4%.

Quality control. CVs for the indicated number split samples were as follows: free testosterone = 11.9%, n = 16; SHBG-bound testosterone = 7.5%, n = 16; testosterone = 16.1%, n = 15; estrone sulfate = 31.9%, n = 14; SHBG = 22.2%, n = 16; DHEAS = 13.4%, n = 10; FSH = 19.1%, n = 16; and LH = 15.9%, n = 16.

We obtained external quality control standards for steroid hormone assays from the College of American Pathologists

(Northfield, IL). For internal quality control, we prepared a single batch of each of the quality control materials, antisera, and tracers for the assay of these analyses for all assays during the study.

Data Analysis

Demographics and fish consumption habits. The age of each subject at time of interview was calculated by subtracting the date of birth from the date of interview. The body mass index (BMI) was calculated by dividing each particpant's weight (kilograms) by the square of his/her height (square meters). Summary measures of fish consumption habits included number of total GL sport fish meals consumed and duration of consumption, as well as total years eating any sport fish. The total Great Lakes sport-caught fish (GLSCF) meals variable was the sum of the number of different types of GL sport fish consumed in the last year and is presented as the mean of the sum for all participants. Information was obtained about the number of years the participants had consumed sport and GL sport fish and is summarized as the average number of years the subject consumed each type of sport fish.

Statistical analysis. We evaluated the normality of the distribution of continuous variables using Shapiro-Wilk W tests. The variables total PCB, lipid-adjusted total PCB, DDE, free testosterone, FSH, SHBG, LH, DHEAS, and BMI were transformed to a natural log scale for all analyses to satisfy normality criteria. Other non-normal variables, which did not meet normality criteria with transformation, were transformed into ranks before analysis: total GLSCF meals; years eating GLSCF; years eating sport-caught fish (SCF); estrone sulfate; testosterone; T_3 in males; and TSH in males.

Proportional differences in categorical variables were evaluated using chi-square tests or Fisher's Exact tests, as appropriate. For continuous variables, we compared means using Student's *t*-tests or analysis of variance with the least-significant-difference method for multiple pairwise comparisons. Adjusted mean hormone levels, controlling for age, BMI, and use of antilipemic, antihypertensive, and nonsteroidal anti-inflammatory medications, were evaluated using two methods. First, differences in hormone levels for males versus females in each fish consumption group were assessed by multiple regression analysis with dummy variables for fish consumption group, male GLSCF consumers, and male referents. Then, sex-stratified comparisons of hormone levels by fish consumption group were estimated using least-squares means from general linear models, which included a dummy variable for fish consumption group.

Pearson partial correlation coefficients were used to evaluate the relationships of serum hormone concentrations with serum lipid-adjusted PCB and DDE concentrations as well as with fish consumption measures, adjusting for age, BMI, and use of antilipemic, antihypertensive, and nonsteroidal anti-inflammatory medications. Further adjustments were made for other possible confounding variables: alcohol consumption and cigarette smoking at the time of blood draw in both sexes; and menopausal status, number of live births since 1970, total weeks of breast-feeding since 1970, and number of children breast-fed since 1970 in females only. Additional analyses were performed omitting the four persons with liver disease (three males, one female) and the four persons with the highest thyroid hormone values (three males, one female), as well as stratified comparisons for premenopausal and postmenopausal women, and for men and women with BMIs above and below the median level.

We used logistic regression analysis for the entire group of 309 participants who responded to the initial five-question screener questionnaire to determine if PCB, DDE, or fish consumption levels, after controlling for age, BMI, and sex, significantly affected odds of having preexisting thyroid disease. Mean levels of PCB, DDE, or fish consumption, adjusted for sex, in cohorts with and without thyroid disease were estimated using least squares means from general linear models.

CVs for hormone split samples were computed as the technical error/mean. Technical error was estimated by $(\Sigma di^2/2n)^{1/2}$, where *di* was the difference in value between the two identical samples and *n* was the number of pairs of split samples.

Results

Demographics, Fish Consumption, PCB Levels, and DDE Levels

On average, male GLSCF consumers were older; had higher BMIs; higher levels of total PCB, total lipid-adjusted PCB, and DDE; and more years of eating SCF and GLSCF than female GLSCF consumers (Table 1). Although the mean quantity of GLSCF meals consumed in the last year was higher in male than in female GLSCF consumers, this difference was not significant. Male and female GLSCF consumers had higher total PCB, total lipid-adjusted PCB, and DDE levels than referent males and females, respectively.

Potential Confounders

Age was positively correlated with years of eating GLSCF and SCF in males and females, and with total PCB and DDE in males only (Table 2). BMI was negatively correlated with total PCB and DDE in females, and positively correlated with total PCB, DDE, and total GLSCF meals in males (Table 2). The negative associations in females were no longer significant when the referent group was excluded (not shown). In both males and females, total PCB and DDE levels were highly correlated with each other and with years eating GLSCF, years eating SCF, and total GLSCF meals.

In males, age was positively correlated with TSH, SHBG-bound testosterone,

Table 1. Mean age, BMI, total serum PCB, lipid-adjusted PCB and DDE levels, and fish-eating habits in study participants.

	Mean for males GLSCF		Mean for females GLSCF	
Characteristic	Consumers	Referents	Consumers	Referents
Age (years)	49.7[a]	47.7	46.6[a]	44.6
(*n*)	(150)	(28)	(42)	(9)
BMI (kg/m^2)[b]	27.4[a]	26.3[c]	23.3[a,c,d]	26.5[d]
(*n*)	(150)	(28)	(40)	(9)
Total PCB (ppb)[b]	4.7[a,e,f]	1.4[c,e]	2.6[a,c,d]	0.9[d,f]
(*n*)	(151)	(28)	(42)	(9)
DDE (ppb)[b]	4.6[a,e,f]	2.0[c,e]	3.3[a,c,d]	1.2[d,f]
(*n*)	(151)	(28)	(42)	(9)
Total lipid-adjusted PCB (ppb)[b]	822.2[a,e,f]	201.1[e]	304.9[a,d]	157.1[d,f]
(*n*)	(31)	(28)	(8)	(9)
Total lipids (mg/dL)	802.7	730.6	640.6	627.7
(*n*)	(31)	(28)	(8)	(9)
Years eating GLSCF	27.8[a]	NA[g]	21.6[a]	NA
(*n*)	(146)		(42)	
Years eating SCF	34.0[a]	NA	25.9[a]	NA
(*n*)	(147)		(42)	
Total GLSCF meals	44.6	NA	32.7	NA
(*n*)	(141)		(35)	

[a]Male GLSCF consumers significantly different from female GLSCF consumers. [b]Geometric mean. [c]Female GLSCF consumers significantly different from referent males. [d]Female GLSCF consumers significantly different from referent females. [e]Male GLSCF consumers significantly different from referent males. [f]Male GLSCF consumers significantly different from referent females. [g]NA; referents were selected because they did not eat GLSCF in 12 months prior to interview. $p < 0.05$ for all significant differences by analysis of variance with least significant difference method for pairwise means.

SHBG, and FSH and negatively correlated with DHEAS and estrone sulfate, while BMI was negatively correlated with SHBG, SHBG-bound testosterone, and testosterone (not shown). Male participants taking antilipemic medication had decreased SHBG-bound testosterone and SHBG. Female participants taking antihypertensives had significantly increased T_3, and males taking antihypertensives had significantly increased free testosterone and decreased SHBG-bound testosterone. Female participants taking nonsteroidal anti-inflammatory medication had increased T_4 and FTI. Thus, in further analyses, means and correlation coefficients were adjusted for age, BMI, and medication usage.

Hormones by Fish Consumption

Mean and adjusted mean thyroid hormone levels are shown in Table 3. In the GLSCF consumer group, males had significantly higher levels than females of unadjusted and adjusted mean T_3, FTI, and T_3 uptake, as well as a higher proportion above reference range for T_3 uptake (Table 3). Males also had significantly lower levels of unadjusted TSH than females. In the referent participants, males had significantly higher adjusted mean T_3 than females (Table 3). Because of differences in thyroid hormones between males and females, analyses were stratified by sex.

Female GLSCF consumers had lower unadjusted mean T_4 and FTI and lower adjusted mean FTI compared to referent females. In males, adjusted and unadjusted mean T_3 uptake and the proportion with T_3 uptake above the reference range were higher in the GLSCF consumers than in the referent males (Table 3). Unadjusted and adjusted mean steroid hormone concentrations in males were similar in GLSCF consumers and referents, with the exception of SHBG-bound testosterone, which was higher in referents (Table 4).

Table 2. Correlations among study participants.

	Pearson correlation coefficient (*r*)					
Characteristic, sex	BMI	Total PCB	Total DDE	Years eating GLSCF	Years eating SCF	Total GLSCF meals
Age (years)						
Female	–0.22	0.03	0.07	0.30*	0.29*	0.23
Male	0.11	0.34*	0.39*	0.24*	0.33*	0.15
BMI (kg/m^2)						
Female		–0.43[a,*]	–0.34[a,*]	–0.27	–0.21	–0.24
Male		0.15*	0.22*	0.13	0.04	0.25*
Total PCB (ppb)						
Female			0.59*	0.57*	0.43*	0.51*
Male			0.69*	0.34*	0.35*	0.51*
DDE (ppb)						
Female				0.47*	0.39*	0.46*
Male				0.22*	0.26*	0.35*
Years eating GLSCF						
Female					0.81*	0.68*
Male					0.75*	0.55*
Years eating SCF						
Female						0.50*
Male						0.44*

[a]Not significant in GLSCF consumers alone. *$p < 0.05$.

Table 3. Mean serum thyroid hormone concentrations and percent abnormal values in study participants by fish consumption group.

Hormone	Group	No.	Mean[a]	Adjusted mean[b]	Percent below reference range[c]	Percent above reference range
Females						
T_3 (ng/dL)	GLSCF consumers	42	107.3[#]	106.4[#]	0	0
	Referent females	9	111.6[##]	111.2[##]	0	0
T_4 (µg/dL)	GLSCF consumers	42	6.59*	6.52	9.5	0
	Referent females	9	7.83*	7.80	0	0
T_3 uptake (%)	GLSCF consumers	42	32.4[#]	32.5[#]	0	26.2[#]
	Referent females	9	32.9	33.1	0	22.2
FTI	GLSCF consumers	42	2.09*,[#]	2.07*,[#]	4.8	0
	Referent females	9	2.56*	2.56*	0	0
TSH (µIU/mL)	GLSCF consumers	42	2.21[#]	2.25	2.4	7.1
	Referent females	9	1.64	1.54	0	0
Males						
T_3 (ng/dL)	GLSCF consumers	130	127.6[#]	127.7[#]	1.5	3.1
	Referent males	25	139.3[##]	138.5[##]	0	4.0
T_4 (µg/dL)	GLSCF consumers	134	7.12	7.11	8.2	0
	Referent males	25	7.84	7.89	0	4.0
T_3 uptake (%)	GLSCF consumers	134	35.2**,[#]	35.2**,[#]	0	45.5**,[#]
	Referent males	25	32.1**	32.1**	4.0	16.0**
FTI	GLSCF consumers	134	2.44[#]	2.44[#]	6.0	0.8
	Referent males	25	2.50	2.52	0	4.0
TSH (µIU/mL)	GLSCF consumers	144	1.65[#]	1.66	5.6	2.1
	Referent males	26	1.82	1.81	0	3.8

For each sex, test statistics were estimated using Student's *t*-tests for unadjusted means, general linear models for adjusted means, and chi-square or Fisher's exact tests, as appropriate, for percentages.
[a]Arithmetic mean. [b]Adjusted for age, BMI, and antilipemic, antihypertensive, and nonsteroidal anti-inflamatory medications. [c]Normal ranges for thyroid hormones: T_3 = 60–181 ng/dL; T_4 = 4.5–12.5 µg/dL; T_3 uptake = 22–35%; FTI = 1.4–3.8; TSH = 0.5–4.7 µIU/mL. *$p < 0.05$ for female GLSCF consumers compared with female referents. **$p < 0.05$ for male GLSCF consumers compared with male referents. [#]$p < 0.05$ for male GLSCF consumers compared with female GLSCF consumers. [##]$p < 0.05$ for male referents compared with female referents.

Thyroid Hormones by PCB, DDE, and Level of Fish Consumption

Women. In females, T_4 and FTI were negatively correlated with total PCB level after adjustment for age, BMI, and medication use (Table 5). The associations between T_4 and PCB level and FTI and PCB level remained significant with further adjustment for menopausal status, number of live births, weeks of breast-feeding, and number of children breast-fed; alcohol consumption and cigarette smoking; or DDE level. The association of FTI, but not T_4, with PCB level remained significant after adjusting for years eating GLSCF and total GLSCF meals.

T_4 and FTI were also inversely correlated with years of consuming GLSCF, and total GLSCF meals after adjustment for age, BMI, and medications. The associations remained significant with further adjustment for current smoking and alcohol consumption or DDE level. All of these associations, with the exception of the association of T_4 with years eating GLSCF, remained significant after control for reproductive variables. Only the association of FTI with total GLSCF meals remained significant, however, after adjusting for total PCB level.

TSH was positively correlated with total PCB level, but this association did not reach significance (Table 5). However, exclusion of one woman with a TSH value of 11 µIU/mL, which was well above the normal range of 0.5–4 µIU/mL, resulted in a significant partial correlation coefficient ($r = 0.33$, $p = 0.03$). TSH was positively correlated with years of GLSCF consumption after controlling for age, BMI, and medication use and after further control for alcohol and

smoking, reproductive variables, PCB level, or DDE level.

T_3 and T_3 uptake were not significantly correlated with any predictor variable. We found no significant partial correlation coefficients for thyroid hormones with DDE level or years of SCF consumption.

We also examined associations of thyroid hormones with PCB level and with levels of fish consumption in premenopausal and postmenopausal women separately (not shown). FTI remained significantly and inversely associated with PCBs and total GLSCF meals in premenopausal and postmenopausal women and with years eating GLSCF in premenopausal women. The inverse associations of T_4 with years eating GLSCF and with total GLSCF meals remained significant only in premenopausal women. The association of TSH with total GLSCF meals became significant only in postmenopausal women.

The associations with FTI and TSH were similar for women above and below the median BMI (not shown). However, the associations of T_4 with PCBs, years eating GLSCF, and GLSCF meals were stronger in women with BMI below the median level.

Men. In males, T_4 was negatively correlated and T_3 uptake was positively correlated with total PCB level after adjustment for age, BMI, and medications. The relationships remained significant after further adjustment for cigarette smoking and alcohol consumption, DDE level, or fish consumption variables (Table 6). Years of eating SCF was negatively associated with T_4 after controlling for age, BMI, and medication use, as well as after controlling for smoking and alcohol use or DDE level, but not PCB level. TSH was negatively associated with years of GLSCF consumption after adjusting for age, BMI, and medication use and with further adjustment for alcohol and smoking intake or DDE level, but not after further control for PCB level.

FTI and T_3 were not significantly correlated with PCB level, except for T_3 and only when adjusted for alcohol intake and smoking, as well as age, BMI, and medication. Controlling for age, BMI, and medication use, T_3 was negatively and significantly correlated with number of years of sport fish consumption. The association remained significant after further adjustment for smoking and alcohol intake, PCB level, or DDE level.

When three men with high thyroid hormone values (TSH = 10 and 11, normal range = 0.5–4.7 μIU/mL, and T_3 = 309, normal range = 10–181 ng/dL) were removed from the data set, partial correlation coefficients for all thyroid hormones retained similar significance levels. All correlations remained significant after excluding the three men with liver disease, except the association between T_4 and years of eating SCF. There were no significant partial correlations found for thyroid hormones with DDE level. T_4 and T_3 uptake were significantly associated with total GLSCF meals only after adjustment for alcohol and smoking, age, BMI, and medications.

We also examined associations of thyroid hormones for men with BMI above and below the median (not shown). The association of PCBs with T_4 and T_3 uptake remained significant only for men with low BMI. Associations of TSH and T_3 with fish variables were of similar magnitude, but no longer significant after stratification.

Steroid Hormones by PCB, DDE, and Level of Fish Consumption in Men

SHBG-bound testosterone was significantly and negatively correlated with PCB level in males after adjustment for age, BMI, and medications and also upon further control for cigarette smoking and alcohol consumption, fish consumption variables, or DDE level (Table 7). Testosterone was significantly associated with PCB level only after control for total GLSFC meals, years eating GLSCF, age, BMI, and medication.

Testosterone was positively correlated with total GLSCF meals after adjusting for age, BMI, and medications. It remained significant after adjustment for PCB or DDE levels, but not after adjustment for smoking and alcohol intake. SHBG-bound testosterone was significantly and negatively correlated with years of consuming SCF after adjusting for age, BMI, and medications, and with further adjustment for smoking and alcohol intake or DDE level, but not PCB level. SHBG-bound testosterone became significantly and negatively associated with years of eating GLSCF and total GLSCF meals only after adjusting for current smoking and alcohol intake, and age, BMI, and medication use, or after omitting the three persons with liver disease.

Table 4. Mean serum steroid hormone concentrations by fish consumption group in male participants.

Hormone	Group	No.	Mean[a]	Adjusted mean[a,b]
Estrone sulfate (pmol/mL)	GLSCF consumers	146	1.94	1.95
	Referent males	27	2.01	1.92
FSH (mIU/mL)	GLSCF consumers	151	3.48	3.45
	Referent males	28	3.00	3.16
LH (mIU/mL)	GLSCF consumers	150	2.59	2.58
	Referent males	27	2.29	2.31
DHEAS (μmol/L)	GLSCF consumers	133	7.75	7.85
	Referent males	20	9.39	8.60
SHBG (nmol/L)	GLSCF consumers	151	35.4	35.4
	Referent males	28	36.1	36.0
Testosterone (ng/dL)	GLSCF consumers	147	408.2	411.1
	Referent males	26	390.5	375.7
SHBG-bound testosterone (%)	GLSCF consumers	151	27.6*	27.6*
	Referent males	28	30.2*	30.1*
Free testosterone (%)	GLSCF consumers	149	2.76	2.76
	Referent males	28	2.86	2.85

Test statistics were estimated using Student's *t*-tests for unadjusted means and general linear models for adjusted means. [a]Arithmetic mean for estrone sulfate, testosterone, and SHBG-bound testosterone; geometric mean for FSH, LH, DHEAS, SHBG, and free testerosterone. [b]Adjusted for age, BMI, and antilipemic, antihypertensive, and nonsteroidal anti-inflamatory medications (least-squares means from general linear model). *$p < 0.05$ for GLSCF consumers compared with referents.

Table 5. Partial correlation coefficients for thyroid hormones with PCB, DDE, and fish consumption levels in female participants, adjusted for age, BMI, and medications.

Hormone		PCB	DDE	Years eating GLSCF	Years eating SCF	Total GLSCF meals
T_3 (ng/dL)	r[a]	–0.06	0.00	–0.07	0.00	–0.17
	n	49	49	49	49	42
T_4 (μg/dL)	r	–0.38*[b,c,d,e,f]	–0.10	–0.33*[c,d,e,f]	–0.13	–0.36*[b,c,d,e,f]
	n	49	49	49	49	42
FTI	r	–0.53*[b,c,d,e,f,g]	–0.14	–0.40*[b,c,d,e,f]	–0.18	–0.51*[b,c,d,e,f,h]
	n	49	49	49	49	42
T_3 uptake (%)	r	–0.07	–0.03	–0.02	–0.10	–0.10
	n	49	49	49	49	42
TSH (μIU/mL)	r	0.18[e]	0.04	0.34*[b,c,d,e,f,h]	0.17	0.25
	n	49	49	49	49	42

[a]Partial correlation coefficient adjusted for age, BMI, and antilipemic, antihypertensive, and nonsteroidal anti-inflamatory medications. [b]Significant when further adjusted for reproductive factors (number of live births, number of children breast-fed, weeks of breast-feeding, and completion of menopause). [c]Significant when further adjusted for current smoking and alcohol consumption. [d]Significant when further adjusted for DDE level. [e]Significant after elimination of the participant with high TSH. [f]Significant after elimination of three participants with liver disease. [g]Significant when further adjusted for years eating GLSCF and total GLSCF meals. [h]Significant when further adjusted for PCB level. *$p < 0.05$ for partial correlation coefficients adjusted for age, BMI, and medications.

In unstratified analyses, estrone sulfate, SHBG, FSH, DHEAS, and LH were not significantly associated with PCBs, DDE, or fish consumption levels after controlling for confounders. We also examined associations of thyroid hormones for men with BMI above and below the median (not shown). In men with low BMI, but not high BMI, the association of testosterone with total GLSCF meals and the inverse associations of SHBG-bound testosterone with PCBs and years eating GLSCF were significant, whereas the inverse association of SHBG-bound testosterone with years eating SCF was of borderline significance. Estrone sulfate became inversely and significantly associated with PCBs only in men with low BMI.

Table 6. Partial correlation coefficients for thyroid hormones with PCB, DDE, and fish consumption levels in male participants, adjusted for age, BMI, and medications.

Hormone	PCB	DDE	Years eating GLSCF	Years eating SCF	Total GLSCF meals
T_3 (ng/dL)					
r[a]	–0.09[b]	0.03	–0.01	–0.19*[b,c,d,e,f]	–0.08
n	154	154	150	151	145
T_4 (µg/dL)					
r	–0.20*[b,d,e,f,g]	–0.10	–0.13	–0.17*[b,d,f]	–0.15[b]
n	158	158	154	155	149
FTI					
r	–0.10	–0.05	–0.09	–0.11	–0.08
n	158	158	154	155	149
T_3 uptake (%)					
r	0.24*[b,d,e,f,g]	–0.13	0.12	0.15	0.15[b]
n	158	158	154	155	149
TSH (µIU/mL)					
r	–0.10	–0.06	–0.17*[b,d,e,f]	–0.08	–0.07
n	169	169	165	166	160

[a]Partial correlation coefficient adjusted for age, BMI, and antilipemic, antihypertensive, and nonsteroidal anti-inflamatory medications. [b]Significant when further adjusted for current smoking and alcohol consumption. [c]Significant when further adjusted for total PCB level. [d]Significant when further adjusted for DDE level. [e]Significant after elimination of three participants with liver disease. [f]Significant after elimination of three participants with high thyroid hormones. [g]Significant when further adjusted for years eating GLSCF and total GLSCF meals. *$p < 0.05$ for partial correlation coefficients adjusted for age, BMI, and medications.

Table 7. Partial correlation coefficients for steroid hormones with PCB, DDE, and fish consumption levels in male participants, adjusted for age, BMI, and medications.

Hormone	PCB	DDE	Years eating GLSCF	Years eating SCF	Total GLSCF meals
Testosterone (ng/dL)					
r[a]	–0.10[b]	–0.08	0.03	0.13[c]	0.19*[c,d,e]
n	172	172	168	169	163
SHBG-bound testosterone (%)					
r	–0.23*[b,d,e,f]	–0.08	–0.15[e,f]	–0.17*[d,e,f]	–0.14[e,f]
n	178	178	174	175	169
Free testosterone (%)					
r	0.10	0.02	–0.04	–0.03	0.05
n	176	176	172	173	167
Estrone sulfate (pmol/mL)					
r	–0.07	–0.04	–0.05	0.00	–0.05
n	172	172	168	169	163
FSH (mIU/mL)					
r	–0.05	0.00	–0.08	0.07	0.04
n	178	178	174	175	169
LH (mIU/mL)					
r	–0.08	–0.04	0.03	0.08	–0.03
n	176	176	172	173	167
DHEAS (µmol/L)					
r	0.02	0.00	0.10	0.06	0.00
n	152	152	149	149	145
SHBG (nmol/L)					
r	–0.10	–0.01	–0.02	–0.04	0.03
n	178	178	174	175	169

[a]Partial correlation coefficient adjusted for age, BMI, and antilipemic, antihypertensive, and nonsteroidal anti-inflamatory medications. [b]Significant when further adjusted for years eating GLSCF and total GLSCF meals. [c]Significant when further adjusted for PCB level. [d]Significant when further adjusted for DDE level. [e]Significant after eliminating three participants with liver disease. [f]Significant when further adjusted for current smoking and alcohol consumption. *$p < 0.05$ for partial correlation coefficients adjusted for age, BMI, and medications.

Lipid, Dioxin, and Furan Adjustment

For the small subgroup for whom data was available, there were no substantial differences in the magnitude of correlations of thyroid or steroid hormones with PCBs versus lipid-adjusted PCBs, nor were relationships with PCBs altered after adjustment for dioxins, furans, or coplanar PCBs (data not shown).

Thyroid Disease

We performed the above analyses after eliminating all subjects with a history of thyroid disease. We examined associations of history of thyroid disease (15.0% women and 3.2% men) with PCB and fish consumption in the subjects who responded to the original invitation to participate in the study by completing the five-question screening form. The results (data not shown) indicate that persons with high GLSCF intake in the year before blood collection were somewhat less likely to have a history of thyroid disease after controlling for age, sex, and BMI ($p = 0.053$). No relationship was seen with serum PCB or DDE level, nor was any relationship seen with total years eating GLSCF or SCF.

Discussion

Results from this study suggest that PCB exposure and Great Lakes fish consumption are associated with decreased levels of T_4 and FTI. The relationships overall are stronger in women than in men. Fish consumption, but not PCB exposure, is also significantly associated with decreased levels of T_3 in men. The effects on TSH are variable, with years of Great Lakes fish eating positively associated with TSH in women and negatively associated with TSH in men, suggesting the possibility of two different, sex-specific mechanisms.

This is, to our knowledge, the first study showing an effect of PCB exposure on thyroid function in Great Lakes fish eaters. Two previous studies of exposure through fish consumption in the Netherlands also found decreases in thyroid hormones in infants whose mothers were exposed to PCBs when they were pregnant (*4,5*). In one of the studies (*4*), however, exposure was associated with lower T_4 levels at 2 weeks and higher TSH levels at 2 weeks and 3 months, whereas in the other study (*5*) exposure was associated with higher, not lower, T_4 at 1 and 11 weeks and with higher TSH at 11 weeks. Exposure to high levels of mixed PCBs and furans through rice oil contamination (*2*) has been associated with elevated T_3 and T_4, without changes in TSH or FTI. However, in a more recent study among 160 North Carolina children whose mothers were exposed to PCBs during pregnancy (with *in utero* PCB exposure estimated with the mother's PCB levels in milk and blood),

the umbilical cord sera was not significantly related to total T_4, FTI, or TSH (*6*).

Osius et al. (*3*) noted inverse associations of non-coplanar PCBs with free T_3, a positive association of the mono-*ortho* PCB 118 with TSH, and no associations with T_4 among second-grade school children living near an industrial waste site in Germany. Two other studies found increased thyroid volume after PCB exposure (*26,27*). Langer et al. (*26*) noted increased thyroid volume in 238 employees of a factory that had previously produced PCBs and in 454 adolescents in the surrounding area compared to 572 adults and 965 controls living in less polluted areas. Employees of the factories also had increased prevalence rates of antithyroid antibodies, but not TSH or T_4. Guo et al. (*27*) also noted increased prevalence of goiter in 795 men and women exposed to PCBs and furans in the Yucheng cohort compared with controls. A fourth study found that among women who had miscarried, PCB was inversely related to TSH and positively related to FSH, LH, and prolactin (*28*).

The findings in our study are generally consistent with animal studies which have noted that thyroid function is especially sensitive to PCB exposure. The effects appear to be congener and dose specific. Desauliniers et al. (*29*) found an increase in T_4 at lower PCB doses and a decrease in T_4 at higher PCB doses. The effect was primarily present with the dioxin-like congener PCB-77 and in female animals. At the same doses, there were no effects on testosterone, gonadotropins, or TSH. In a later paper, Desauliniers et al. (*30*) found an increase in T_4 after exposure to estradiol or PCB-153 and a decrease in T_4 after exposure to PCB-126. Similarly, Li et al. (*31*) noted an increase in T_4 with exposure to lower doses (8 mg/kg) and a decrease after exposure to ≥ 24 mg/kg purified PCB-110. The magnitude of thyroid change is related to laterality of chlorine substitution of individual congeners and the relation of the chlorines to hydroxylated metabolites (*32*). Mechanisms by which PCBs have reduced T_4 in animals include increased glucuronidation, decreased binding to transthyretin, and increased conversion of T_4 to T_3 by 5′diodinases (*33–38*).

In the current study, associations of thyroid hormones with fish consumption are similar to associations of thyroid hormones with PCB levels, although there are some notable differences. The negative associations of T_3 with eating fish but not with PCBs, the inconsistent associations of PCBs and fish consumption with TSH, and the insignificant association of fish consumption but not PCB level with history of thyroid disease suggests that separate mechanisms may be operative.

In males, there were no significant associations in unstratified analyses of either PCB level or years of fish consumption with free testosterone, estrone sulfate, FSH, LH, DHEAS, or SHBG, after controlling for age, BMI, and medication. Testosterone, however, was significantly associated with total GLSCF meals, and SHBG-bound testosterone was inversely associated with PCB level and years of consuming SCF. We found similar results in a cohort of workers exposed to higher levels of PCBs than in the current study (*39*); in that cohort, SHBG and percent SHBG-bound estradiol were decreased in women with higher PCB levels. We found no differences in SHBG in men (*39*). The fact that SHBG levels in the current study are not generally elevated suggest that PCBs may affect binding to SHBG rather than affecting the levels of the binding protein.

Associations of hormone levels with PCBs and fish consumption persisted after control for BMI. There was evidence, however, of possible effect modification with selected associations that were stronger in persons with lower BMI, perhaps reflecting variations in PCB metabolism as noted with polybrominated biphenyls in previous studies (*40*).

Despite a strong correlation between PCB and DDE levels, DDE was not associated with changes in any hormone in either males or females after controlling for confounders. Previous literature of effects of DDE on thyroid hormones is sparse. In a previous study Gerhard et al. (*28*) found an inverse association of DDE with TSH and a positive association with estradiol among 89 women who had miscarried.

Although associations of thyroid hormones with PCB levels and fish consumption were significant in the current study, only a small percent of measurements had values outside the reference range. The sample was selected, however, for persons without a history of thyroid disease. The percentages of subjects with known thyroid disease on the screening questionnaire (15% in women and 3.2% in men) is similar to prevalence rates seen in previous studies (*41–43*). Bagchi et al. (*41*) noted that 11.25% of women and 6.2% of men over 55 years of age had abnormal thyrotropin levels; Vanderpump et al. (*42*) noted that 13.2% of women and 1.5% of men (average age 58 years) were either hypothyroid or hyperthyroid; and Helfand and Redfern (*43*) found that 9.5% of 40- to 60-year-old women had previously unsuspected but overt thyroid dysfunction. The similarity of our prevalence rates with previous studies, as well as the lack of differences among exposure groups in values out of range, support the subtle nature of effects observed in this study.

Limitations to this study include those inherent in any cross-sectional study, including imprecise estimates of exposure to PCBs and other contaminants such as dioxins, as well as the small number of hormones that can be studied in women who did not report menstrual histories at the time of blood drawing. In addition, there is the possibility that the inverse association of T_4 with PCBs is really confounded by lipid levels, which were not measured in the entire group and are known to be inversely associated with T_4 and positively associated with PCBs, either through direct hepatotoxicity or partitioning of PCBs in fatty tissue (*44,45*). The fact that lipid adjustment did not alter the magnitude of associations in the subgroup of persons for whom lipids were available suggests that this is unlikely to be a major confounder. Quality control for individual hormones varied with split samples for thyroid hormones, testosterone, SHBG, DHEAS, FSH, and LH having substantially lower CVs than split samples for estrone sulfate. Results for estrone sulfate, because of lower precision of the measurements, could therefore be biased towards the null hypothesis. Nevertheless, our findings are consistent with previous studies and suggest that exposure to low levels of PCBs through contaminated fish exposure may have subtle effects on hormonal balance. Delineation of specific effects of fish exposure, other than through elevations of PCBs, await further studies.

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