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Thyroid hormones are associated with exposure to persistent organic pollutants in aging residents of upper Hudson River communities

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Abstract

The aim of this study was to evaluate the association between persistent organic pollutants (POPs), and thyroid hormones in an aging population. Forty-eight women and 66 men, aged 55 to 74 years and living in upper Hudson River communities completed a questionnaire and provided blood specimens. Serum was analyzed for thyrotropin (thyroid stimulating hormone, TSH), free (fT₄) and total thyroxine (T₄), total triiodothyronine (T₃), and for POPs. POPs included 39 polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) determined by gas chromatography with electron capture detection (GC-ECD), and nine polybrominated diphenyl ethers (PBDEs) determined by high-resolution gas chromatography with high-resolution mass spectrometry detection (HRGC-HRMS). Multivariable linear regression analysis was used to evaluate associations between thyroid hormones and sums of POPs, adjusted for covariates and stratified by sex. Effects were expressed as differences in thyroid hormone levels associated with a doubling in the level of exposure. Among women, DDT+DDE increased T₄ by 0.34 µg/dL (P=0.04) and T₃ by 2.78 ng/dL (P=0.05). Also in women, sums of PCBs in conjunction with PBDEs elicited increases of 24.39-80.85 ng/dL T₃ (P<0.05), and sums of PCBs in conjunction with DDT+DDE elicited increases of 0.18-0.31 µg/dL T₄ (P<0.05). For men estrogenic PCBs were associated with a 19.82 ng/dL T₃ decrease (P=0.003), and the sum of estrogenic PCBs in conjunction with DDT+DDE elicited an 18.02 ng/dL T₃ decrease (P=0.04). Given age-related declines in physiologic reserve, the influence of POPs on thyroid hormones in aging populations may have clinical implications and merits further investigation.

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Keywords

Aging; dichlorodiphenyldichloroethylene (DDE); persistent organic pollutants (POPs); polybrominated diphenyl ethers (PBDEs); polychlorinated biphenyls (PCBs); thyroid hormones

Introduction

A competent hypothalamus-pituitary-thyroid (HPT) axis is essential for proper cardiovascular (Klein and Ojamaa, 2001) and neurocognitive function (Liappas et al., 2009). A growing literature suggests that low-level exposures to persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) and its primary metabolite and breakdown product dichlorodiphenyldichloroethylene (DDE), and polybrominated diphenyl ethers (PBDEs), disrupt the human HPT-axis; however, the clinical implications are questionable (Boas et al., 2012; Hagmar, 2003; Salay and Garabrant, 2009). These chemicals were used for a wide variety of industrial and commercial purposes: PCBs were employed as industrial heat sinks and lubricants, and in commercial caulking materials and fluorescent light ballasts (ATSDR, 2000); DDT was used to control insect pests (ATSDR, 2002); and PBDEs were blended into myriad products to impart flame resistance (ATSDR, 2004). These compounds are no longer employed in the U.S. (i.e., PCBs and DDT), or their use is being phased-out (i.e., PBDEs), but persistence in the environment and long 1/2-lives *in vivo* result in ongoing exposure to the general population; detectable levels are measured in the vast majority of human specimens collected for biomonitoring purposes (CDC, 2009).

Several groups have considered the effects of thyroid function and non-occupational exposure to POPs in human populations (Hagmar, 2003; Salay and Garabrant, 2009), but few have done so specifically among aging individuals. The current study was designed to help address this research gap. Aging populations are at greater risk for subclinical deviations in thyroid function, and possibly an increased risk for overt disease (Peeters, 2008). Older individuals are also likely to be at greater risk from exposure due to age-related declines in hepatic metabolism and biliary and renal excretion, in addition to a reduced ability to compensate for toxicologic insults, or decreased physiologic 'reserve' (Geller and Zenick, 2005). Furthermore, birth cohort effects make aging individuals more likely to have experienced sustained exposures to POPs at higher levels than younger individuals, as their life-experience predates the 1972 and 1979 U.S. bans for use of DDT and PCBs, respectively. The objective of this study was to evaluate the association between PCBs, DDT and DDE, and PBDEs, on thyroid hormones in aging women and men residing in close proximity to PCB-contaminated sections of the Hudson River. It is part of a larger investigation of POP exposure and neurocognitive status in the elderly (Fitzgerald et al., 2008; Fitzgerald et al., 2012).

Methods

Sample Selection

Recruitment for this cross-sectional study was previously described in detail (Fitzgerald et al., 2008). In brief, the sampling frame comprised 2704 women and men 55 to 74 years of age, residing for ≥ 25 years in one of three New York State (NYS) towns: Hudson Falls, Fort Edwards or Glens Falls (Figure 1). This area was selected as the study setting because the original focus of the parent project was PCBs, and from 1947 to 1977 two General Electric plants in this area used PCBs in the manufacture of electrical capacitors; nearly 500,000 kg of PCBs were discharged from these facilities into the upper Hudson River (EPA, 2011). In 1983, the U.S. EPA classified a 322 km section from Hudson Falls to New York City as a

National Priority List Superfund site. Individuals were identified using online telephone directories and Department of Motor Vehicles records, supplemented by a business marketing database, comprised of basic demographic data, purchased from infoUSA® (InfoUSA.com, Papillion, NE USA). Potential participants were selected randomly and contacted by telephone to schedule an interview. Individuals reporting 1 year of occupational PCB exposure, a history of severe head injury, or a diagnosis of neurologic disease were excluded to facilitate the initial investigation of neurocognition. Participants were uniformly recruited from 2000 to 2002 and completed an inhome, interviewer-administered study questionnaire. The study protocol was approved by the Institutional Review Board of the NYS Department of Health (DOH), and all study participants provided informed consent prior to enrollment. A total of 126 women and 127 men agreed to participate for an overall response proportion of 40% among those who were eligible and invited.

Chemical Analysis

Within two weeks of questionnaire completion participants visited the Occupational Health Clinic in Glens Falls and provided 25 mL of fasting venous blood, which was collected into red-top evacuated glass tubes without a preservative. The blood was centrifuged yielding approximately 10 mL serum analyzed between 2001 and 2003 for PCBs, DDT and DDE at the Wadsworth Center, NYS DOH according to previously described procedures (Fitzgerald et al., 2007). In brief, 39 PCB congeners, including IUPAC #s 28, 52, 60, 66, 74, 77, 81, 95, 99, 101, 105, 110, 114, 118, 123, 126, 130, 138, 146, 153, 156, 157, 167, 169, 170, 172, 177, 178, 180, 183, 187, 189, 193, 194, 199, 201, 203, 206 and 209, p, p'-DDT and p, ' -DDE were measured in 2 mL of sera using dual column capillary gas chromatography with micro-electron capture detection (GC-ECD). Thirty PCB congeners were determined in a primary analysis, followed by determination of nine additional congeners in a secondary analysis using residual serum. Ten participants providing <25 mL of blood had insufficient remaining serum volume for the secondary analysis and so had missing values for nine congeners (#s 77, 81, 95, 114, 123, 126, 157, 169 and 189). The limit of detection (LOD) was determined using target analytes representing tri- (#28), penta- (#118), hexa- (#s 138 and 153) and hepta- (#s 170 and 180) biphenyls, and p,p'-DDE. Newborn calf serum was spiked at 0.17 ng/mL and seven replicates were extracted and analyzed. The standard deviation of seven replicates multiplied by the t-factor 3.14 was used to calculate the LODs ranging from 0.01 to 0.04 ng/mL, and an average LOD equal to 0.02 ng/mL. Congeners were *a priori* operationalized as five POP sums including: 1) PCB₁, all 39 measured PCB congeners; 2) PCB₂, 12 'thyroid like' PCB congeners (#s 28, 52, 60, 74, 77, 95, 99, 101, 105, 114, 118 and 126) likely to compete for binding to serum thyroid hormone transport proteins (Chauhan et al., 2000); 3) PCB₃, 12 'anti-estrogenic' PCB congeners (#s 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189) with aryl-hydrocarbon receptor activity (Van den Berg et al., 2006); 4) PCB₄, seven 'estrogenic' PCB congeners (#s 52, 77, 95, 99, 101, 110 and 153) with evidence *in vitro* or *in vivo* (Cooke et al., 2001); and 5) DDT, DDT+DDE. Any remaining serum was stored at -20 °C.

In 2005 the study was expanded to include PBDEs, which were then analyzed in the residual serum specimens according to a previously described procedure (Fitzgerald et al., 2010). In brief, nine PBDE congeners, including IUPAC #s 28, 47, 66, 85, 99, 100, 138, 153 and 154 were determined in 1 mL serum using high resolution gas chromatography with high resolution mass spectrometry (HRGC/HRMS). A series of quality control samples were processed with each batch of 20 samples, including surrogates, method blanks, matrix spikes, duplicates and standard reference materials. Surrogate standards consisting of serum samples spiked with ¹³C-labeled PBDEs were used to assess recovery. LODs were determined as three standard deviations above the mean of method blanks, and ranged from

1 to 20 pg/mL contingent on congener and sample volume. The sum of PBDE congeners was operationalized as BDE.

Data were reported as wet-weight values. For determinations below the LODs, machine-read values were employed with no substitution to preclude the introduction of bias that has been demonstrated using that approach (Schisterman et al., 2006). The laboratories at the Wadsworth Center participate in the Arctic Monitoring and Assessment Program's proficiency testing program (AMAP). Tests are administered quarterly by Centre de Toxicologie du Québec, Canada, and reported results are scored either "satisfactory," "qualified" or "unsatisfactory." The laboratory received "satisfactory" scores for PCB congeners and organochlorine pesticides measured in serum during the analysis period for the current study. Satisfactory scores were also obtained for measurement of PBDE congeners in serum during that time.

Thyroid Hormone and Lipid Analysis

Serum was also analyzed in 2005 for thyroid hormones by the Clinical Chemistry Laboratory, Wadsworth Center, NYS DOH. The laboratory is CLIA '88 accredited and participates in numerous external quality assurance (proficiency testing) programs. The laboratory was blinded to all exposure data. Thyroid function biomarker concentrations including thyrotropin (thyroid stimulation hormone, TSH), free (fT₄) and total thyroxine (T₄) and total triiodothyronine (T₃) were measured using a Roche Elecsys 1010 system immunoelectrochemiluminometric assay (Roche Diagnostics, Indianapolis, IN USA). Serum cholesterol and triglycerides concentrations were determined by an enzymatic approach (Allain et al., 1974; Kohlmeier, 1986), employing a Hitachi 911 analyzer (Roche Diagnostics). Average inter-run coefficients of variation were: TSH, 2.5% [5.1% at concentrations <0.2 µIU/mL]; fT₄, 2.2%; T₄, 4.5%; T₃, 5.9%; cholesterol, 1.3%; and triglycerides, 1.9%. Serum total lipids (TL) were estimated as $TL = 2.27 \times \text{cholesterol} + \text{triglycerides} + 0.623$ (Phillips et al., 1989).

Statistical Analysis

All 253 participants had interview and serum PCB data but only 141 of this group had sufficient residual serum available in 2005 for PBDE and thyroid hormone analysis. After excluding 11 participants reporting use of thyroid medications, and another 16 reporting use of sex-hormones (Surks and Sievert, 1995), the final study sample comprised 114 persons.

Descriptive statistics were calculated and distributions examined for demographic factors, medical history and health-behaviors captured by the questionnaire, for thyroid hormones and for POPs. Using a complete-case approach, Spearman correlation coefficients and Kruskal-Wallis tests were used to assess bivariate associations between POPs and thyroid hormones, and with covariates as appropriate. We adjusted POPs for TL as a covariate, to avoid possible bias introduced using a 'traditional' normalization procedure (Phillips et al., 1989; Schisterman et al., 2005). We compared categorical and continuous variables between the 114 participants included in the study sample and the 139 excluded participants using χ^2 -tests or Mann-Whitney U-tests.

Prior to multivariable analysis, a natural log transformation was applied to TSH and POPs following the addition of a constant. Linearity between thyroid hormones and log-transformed POPs was suggested by scatter plots. Sex-stratified (Frederiksen et al., 2009; Hollowell et al., 2002; Laden et al., 1999; Rylander et al., 1997; Schecter et al., 2006) multiple linear regression models were constructed using thyroid hormones as dependent variables, POPs as predictors, and adjusting for covariates. Covariates were *a priori* selected for inclusion as potentially confounding variables based on literature reported associations

with PCBs, DDT, DDE or PBDEs, and with thyroid hormones (Greenland et al., 1999). Participant age (Frederiksen et al., 2009; Hollowell et al., 2002; Laden et al., 1999; Pinkney et al., 1998; Schecter et al., 2006), cigarette smoking, alcohol consumption and socioeconomic status (ATSDR, 2000, 2002, 2004; Kapoor and Jones, 2005) were incorporated. Years of formal education was included to indicate socioeconomic status; missing values for income would have necessitated imputation during regression analysis and the two were correlated ($r=0.46$, $P<0.0001$). We imputed values for nine PCB congeners missing in eight of the participants retained for the final analysis, using a Markov Chain Monte Carlo (MCMC) approach under a missing at random (MAR) assumption (Horton and Kleinman, 2007). Interactions among POP sums were assessed using additional sex-stratified regression models. All effects were expressed as the expected difference in thyroid hormone for a doubling in levels of POPs.

Influential observations were evaluated during regression modeling. Observations were excluded and the analysis repeated where DFFITS >1.5 , DFBETA >1.0 for POPs, or Cook's Distance >1.0 (Kleinbaum et al., 1998). DFFITS and DFBETA measure the influence of individual observations on predicted values and individual regression coefficients, respectively. Cook's distance assesses the influence of individual observations on the overall model fit. SAS v.9.3 (SAS Institute, Inc. Cary, NC USA) was used for all analyses. Statistical significance was defined as $P<0.05$ using two-tailed tests.

Results

Univariate Analysis

Demographic and clinical characteristics for participants included in the study sample are presented in Table 1. The mean age (range) was 63.2 years (55-74); there were 48 women and 66 men. Participants were modestly overweight (mean BMI=28.8 kg/m²), but with substantial variability (range 17.2-49.6 kg/m²). Most participants reported consumption of alcoholic beverages in the 12 months preceding the study (82.5%), with a mean 320.2 drinks consumed among drinkers. A lower proportion reported cigarette smoking in the year prior to the study (14.0%); $n=16$ smokers consumed less than one pack per day on average (0.81 packs/day). A substantial proportion of participants pursued an education beyond secondary school (60.5%), with an overall mean (range) of 13.9 (6-20) years schooling completed. Most participants (70.3%) earned less than \$60,000 per year. One woman and one man each reported history of a thyroid disorder, although were not using thyroid medication at the time of the study and so were retained in the analysis. The 139 participants excluded from the current study were more likely to be female (57.9%, $P=0.03$) and to smoke cigarettes (23.9%, $P=0.05$) than were the 114 participants included in the current study.

Table 2 describes the distributions for thyroid hormones and serum lipids stratified by sex. We compared thyroid hormone values to Wadsworth Center reference intervals. One man was below the reference interval for TSH (0.3-4.2 μ IU/mL), whereas the upper limit for TSH was exceeded in six men and nine women. However, there were no participants outside of the reference intervals for T₄ (5.1-14.1 μ g/dL) or T₃ (80-200 ng/dL). One man was below, and one woman equaled the lower limit of the reference interval for fT₄ (0.9-1.7 ng/dL).

Table 2 also presents sex-stratified POP distributions for participants included in the current study. Overall values for individual congeners can be found in Supplemental Table 1. Supplemental Table 2 provides values for individual congeners and POP sums reported on a lipid-weight basis for comparison to previously published work. Twenty-four PCB congeners were detected in at least 50% of the overall study sample. The overall PCB profile was dominated by #s 153 (median=0.52 μ g/L serum), 180 (0.43 μ g/L serum), 138 (0.42 μ g/L serum), 74 (0.20 μ g/L serum), 118 (0.17 μ g/L serum) and 170 (0.15 μ g/L serum);

their sum accounted for 65% of the overall median sum of 39 measured PCBs (PCB₁; 2.93 µg/L serum). The median sum of thyroid-like PCBs (PCB₂; 0.57 µg/L serum) comprised 19% of PCB₁, the sum of anti-estrogenic PCBs (PCB₃; 0.43 µg/L serum) 15% and the sum of estrogenic PCBs (PCB₄; 0.63 µg/L serum) comprised 22%. The DDT metabolite DDE was measured in the highest median concentration among all POPs (3.36 µg/L serum). Six of nine measured PBDE congeners were detected in more than 50% of participants including; #s 28, 47, 85, 99, 100 and 153. The overall congener profile (median) was dominated by #47 (0.07 µg/L serum), which accounted for 41% of the overall total (BDE; 0.17 µg/L serum). No statistically significant differences were observed between the 114 persons included and the 139 excluded from the current study in POP concentrations, on either a wet-weight or a lipid-weight basis.

Bivariate Analysis

Concentrations of thyroid hormones were similar for women and men (Table 2). A negative association was detected for BMI with fT₄ ($r=-0.20$, $P=0.04$), and for years of education with T₃ ($r=-0.26$, $P=0.01$). Smokers had higher fT₄ ($P=0.01$), T₄ ($P=0.004$) and T₃ ($P=0.01$), yet no dose-response trend was suggested in association with packs smoked among 16 smokers. Two participants reporting a history of thyroid disorder and retained in the analysis had a 0.20 ng/dL lower median fT₄ than those without, albeit not statistically significant ($P=0.08$). Unexpected differences in TSH ($P=0.03$) were detected by area of residence, and differences in T₄ were detected by year of enrollment ($P=0.03$). The differences did not vary according to POPs. We conducted a thorough review of quality control data, specimen processing procedures and specimen collection and storage protocols and could not identify their source. As such, these findings are likely to reflect a chance occurrence due to small sample sizes within strata.

As expected, PCBs₁₋₄ and DDT demonstrated strong inter-correlations ($r=0.74-1.00$, $P<0.0001$), but not with BDE. With the exception of BDE, age was positively correlated to all POPs ($r=0.21-0.32$, $P=0.03$). Women had higher median levels of PCB₂ than men (0.71 vs. 0.52 µg/L serum, $P=0.03$). Associations were not detected for POPs with education, area of residence or year of study participation. No significant bivariate associations were detected for POPs and thyroid hormones among women. Among men, positive associations were detected for TSH with PCB₁ ($r=0.26$, $P=0.05$), PCB₂ ($r=0.37$, $P=0.003$), PCB₄ ($r=0.26$, $P=0.04$) and DDT ($r=0.34$, $P=0.01$). Negative associations were detected for fT₄ with PCB₂ ($r=-0.28$, $P=0.03$) and BDE ($r=-0.32$, $P=0.01$), and for T₃ with PCB₂ ($r=-0.29$, $P=0.02$), PCB₃ ($r=-0.29$, $P=0.03$) and PCB₄ ($r=-0.28$, $P=0.03$) in men.

Multivariable Analysis

Sex-stratified multiple linear regression models were constructed to assess the effects of POPs as predictors of thyroid hormone, adjusted for covariates. No associations were detected for TSH or fT₄ in women (Table 3). However, we detected positive associations for T₄ and T₃ with DDT, respectively equal to differences of 0.34 µg/dL (95% CI 0.01, 0.66) and 2.78 ng/dL (95% CI 0.04, 5.52). These corresponded to 3.9% and 2.3% increases, respectively, from the sex-specific means. Among men (Table 4) inverse associations were detected for fT₄ and T₃ with BDE and PCB₄, equal to differences of -0.03 ng/dL (95% CI -0.06, -0.01) and -19.82 ng/dL (95% CI -32.69, -6.95), respectively, corresponding to 2.4% and 15.7% decreases from the sex-specific means.

Sex-stratified multiple linear regression models were also constructed to assess potential interactions, or heterogeneity of effects, for simultaneous exposure to PBDEs and PCBs or DDT as predictors of thyroid hormones, adjusted for covariates. Table 5 describes overall

effects with P-values provided for statistical interaction terms (i.e., BDE $\times$ PCB₁₋₄ or BDE $\times$ DDT). The concurrent effects of BDE and PCB₁₋₄ in women showed positive departures from multiplicativity, with T₃ differences of 24.52 ng/dL (PCB₁) to 80.24 ng/dL (PCB₃). These corresponded to 20.1%–65.6% increases from the sex-specific mean. In other words, the positive PCBs-T₃ association in the presence of PBDEs was magnified by an increase in the level of PBDEs. The strongest overall effects were detected for the sums of anti-estrogenic PCBs (PCB₃) and estrogenic PCBs (PCB₄). No interactions were detected for BDE among men.

Finally we constructed sex-stratified models to assess potential interactions for concurrent exposure to DDTs and PCBs as predictors of thyroid hormones, adjusted for covariates. Table 6 describes overall effects with P-values again provided for interaction terms (i.e., DDT $\times$ PCB₁₋₄). In women, the concurrent effects of DDT and POP₁₋₃ showed positive departures from multiplicativity, with an fT₄ difference of 0.01 ng/dL (POP₁), corresponding to 0.8% of the sex-specific mean, and for T₄ differences of 0.18 µg/dL (POP₁) to 0.55 µg/dL (POP₂), corresponding to 2.1%–6.3% of the sex-specific mean. The interaction between DDT and POP₄ departed from multiplicativity in a negative fashion, in that a negative association between POP₄ and T₄ in the presence of DDT was attenuated (i.e., made ‘more positive’) by an increase in DDT. An overall –0.27 µg/dL T₄ difference resulted, which corresponded to 3.1% of the sex-specific mean. For men, the concurrent effects of DDT and POP₄ demonstrated a similar negative departure from multiplicativity, eliciting an overall –18.02 ng/dL difference in T₃, a 14.3% decrease from the sex-specific mean.

Discussion

Here we report cross-sectional associations between non-occupational exposure to POPs and thyroid hormones among 114 aging women and men, residing in close proximity to the Hudson River. Our results suggest that exposures to PCBs, DDT and DDE, and PBDEs are associated with circulating thyroid hormone concentrations, with contrasting effects for women and men. Using multivariable analysis, the overall patterns of main effects for women and men demonstrated negative and positive point estimates, respectively, for associations between POPs and TSH, and positive and negative point estimates, respectively, for associations between POPs and fT₄, T₄ and T₃. Several significant associations were detected for fT₄, T₄, and T₃. Furthermore, statistical interactions suggest that concurrent exposure to PBDEs and PCBs elicited multiplicative effects on T₃ levels in women, and that concurrent exposure to DDTs and PCBs elicited multiplicative effects on T₄ in women and T₃ in men.

The POPs-thyroid hormone effects we detected occurred at PCB concentrations higher than those experienced by much of the aging U.S. population. The median sum of 35 PCB congeners reported for 2003–2004 US residents 60 years of age (334.5 ng/g lipid) (Patterson Jr et al., 2009) was approximately 21% lower than for participants in the current study (423.8 ng/g lipid). However, the median U.S. DDE concentration (560.0 ng/g lipid) was similar to our study (Patterson Jr et al., 2009). In contrast, the median PBDE #47 level in this study was only 64% of that reported for 2003–2004 U.S. residents 60 years of age (16.9 ng/g lipid) (Sjodin et al., 2008). Similar to prior reports (Dallaire et al., 2009; Hagmar et al., 2001), PBDEs were generally a fraction of those we measured for PCBs. Still, we detected main effects for BDE on fT₄ among men, and BDE had multiplicative impacts on PCB₁₋₄-T₃ associations in women. Detailed descriptions of the sources of exposure to PCBs (Fitzgerald et al., 2007; Fitzgerald et al., 2011) and PBDEs (Fitzgerald et al., 2010) in this population were published previously

Heterogeneity of effects by sex has been reported by prior epidemiologic investigations of POPs and thyroid hormones, including among aging study participants. Yet, there were little consistency in the results. Among U.S. residents >60 years of age, positive PCB-TSH and negative DDE-T₄ associations were reported for women, whereas a negative PCB-TSH association was reported for men; exposure levels were lower than for the current study (Turyk et al., 2007). At PCB and DDE levels similar to our study, Great Lakes sport fish consumers demonstrated negative PCB-T₄ associations, but a negative PCB-T₃ relation was limited to men (Persky et al., 2001). A study of lakeside communities in Quebec, Canada reported negative PCB-T₃ and DDE-T₃ associations in women, but positive and negative PCB-TSH and PCB-T₄ associations for men, respectively (Abdelouahab et al., 2008). In contrast, no sex-differences were reported from a study of Canadian Inuit exposed to PCB and DDE levels higher than in the our study; significant negative PCB-ft₄ and PCB-T₃ associations were reported for both women and men (Dallaire et al., 2009). PBDE #47 was positively related to T₃ in that study; despite higher PBDE levels we did not detect this congener-specific association (data not shown).

Additional studies considered only men, or included few women. A negative correlation was reported for PBDE #47 and TSH in men consuming Baltic sea fish, yet no association for PCBs, DDT or DDE (Hagmar et al., 2001). In contrast, a positive DDE-TSH association was reported for Swedish men at levels lower than in our study, but no association was detected for PCBs at higher levels (Rylander et al., 2006). There was no association for total PCBs or DDE with ft₄ or TSH in NYS anglers (Bloom et al., 2009), although a congener-specific analysis showed increased ft₄ in association with PCB #170; we did not detect that effect in this work (data not shown). No associations were reported for the sum of nine PBDEs in a smaller substudy (Bloom et al., 2008). A larger study of Great Lakes sport fish consumers described positive associations for PBDEs with ft₄ and T₄, and inverse associations with T₃ and TSH (Turyk et al., 2008). However, no interactions were detected between PBDEs and PCBs.

Associations detected among men in this study, suggesting decreases in thyroid hormone with increased exposure to the sum of estrogenic PCBs (PCB₄) or concurrent exposure to DDT and PCB₄, demonstrated greater overall consistency with the trend towards decreases in circulating hormones reported in the literature than did results for women. The main effects for DDT and the interaction effects for POPs among women in our study suggest increases in total hormone levels, contradicting earlier observations; with the exception of the negative effect detected for the DDT- PCB₄ interaction. No main effects were detected for PCBs or PBDEs in women. The experimental literature suggests DDE is likely to alter thyroid hormone levels by modulation of thyroid receptor synthesis and activities (Liu et al., 2011), whereas PCBs would be more likely to exert an influence by altered hormone synthesis and clearance (Liu et al., 2012). It is interesting to note that the strongest adjusted effects in our study were identified with respect to T₃ among women and men; the largest relative difference in women occurred for the interaction between BDE and the sum of anti-estrogenic PCBs (PCB₃), and that for men was observed for DDT- PCB₄. These effects eclipsed those for PCB₂, the sum of PCBs most likely to bind competitively to transthyretin (TTR), a serum thyroid hormone transport protein that accounts for approximately 10% of total circulating levels (Benvenga, 2005).

Our study detected differences primarily in total thyroid hormone concentrations, T₄ and T₃; we did not observe the associations for TSH reported by previous investigators (Abdelouahab et al., 2008; Hagmar et al., 2001; Rylander et al., 2006; Turyk et al., 2007, 2008). Increases in total thyroid hormones, which primarily reflect a biologically inert protein bound fraction, in the absence of meaningful TSH or ft₄ differences, may indicate altered thyroid hormone serum transport protein levels. Changes in peripheral tissue thyroid

hormone deiodinase activities, the primary source of biologically active hormone, might compensate for increased total hormone concentrations by catalyzing ft_4 within the normal range, and thereby maintaining the patency of the HPT axis (Boas et al., 2012; Surks and Sievert, 1995). The concentration and activity of thyroid binding globulin (TBG) and other thyroid hormone binding proteins change at older ages (Braverman et al., 1966; Hesch et al., 1977), which might also account in part for discrepancies between the results of our study and previous work incorporating younger participants. Inverse associations were detected for concentrations of PCB metabolites with TBG in the study of Canadian Inuits (Dallaire et al., 2009), although no association was detected for PBDEs and TBG in the Great Lakes sport fish eaters study (Turyk et al., 2008). We did not measure serum thyroid hormone binding proteins, and thus we can only speculate as to their potential role in the associations detected. All the women in our study were also post-menopausal, which may contribute to the differences in our findings compared to those of investigators including pre-menopausal women. Age differences might be exacerbated by the POP exposure levels among our participants, which vary from prior work, and from the U.S. population overall.

Participants included in this study tended to be male, to smoke less and to be somewhat younger than those participants excluded from this study, based on the availability of thyroid hormone determinations and use of thyroid and sex hormones. Our data suggest that the sex and age differences are a consequence of excluding women taking thyroid or sex hormones. The difference in cigarette smoking is likely to represent a chance finding given small numbers. If individuals smoking cigarettes were more or less predisposed to differences in thyroid hormones in association with POP exposure then generalizability of these results to the study population may be limited, although the internal validity of our analysis is unlikely to be compromised.

Our study has several additional limitations. Given the small sample size and the need to stratify by sex, we may have had insufficient statistical power to detect associations more subtle than those reported, or to investigate additional factors that might also modify effects. For example, blood glucose was reported as an effect modifier of the PBDE-thyroid association in the Great Lakes study (Turyk et al., 2008), yet our sample included only five women and six men with diabetes. We employed several *a priori* defined grouping strategies, based on predictive biologic activity to evaluate the effects of POPs. An earlier, exploratory, 'congener specific' approach produced instable statistical models, highly susceptible to the influence of individual observations and so was not reported. While this strategy helps to address the inter-correlated nature of POP congeners and to reduce the number of statistical tests, it might also lead to non-detection of very specific associations, in particular given previously reported congener-specific effects (Bloom et al., 2009; Dallaire et al., 2009; Turyk et al., 2008). Still, many independent statistical tests were conducted in our study and consequently some of our findings may have resulted from chance, due to inflation of the type-1 error rate.

We also did not measure the hydroxylated or methylsulfonated metabolites of PCBs and PBDEs, which appear to be most active in competition for thyroid transport protein binding sites and estrogenic activity (Cao et al., 2010; Hamers et al., 2006; Kester et al., 2000; Ren and Guo, 2012). This may have biased our study results by misclassifying exposure, should metabolite levels not have correlated perfectly to parent compound levels; however, we cannot be sure of the direction. In addition, we did not measure polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) or hexachlorobenzene (HCB), other POPs frequently associated with exposure to PCBs and also reported to be associated with thyroid hormones (Boas et al., 2012). Hence, unmitigated confounding may influence our results, and given the likelihood for interactions among various POPs the impact is difficult to predict. Furthermore, our data are cross-sectional by nature, and thus

subject to ‘reverse’ causation bias in that we cannot assess temporality between the exposure to POPs and concentrations of thyroid hormone.

This study offers several strengths including a comprehensive assessment of exposure to various POPs with the capture of detailed confounder data. We report sex-specific interactions between PCBs and PBDEs, and PCBs and DDTs, with respect to thyroid hormone levels in an aging U.S. population. Older individuals are more likely susceptible to toxic insult than younger groups, given enhanced vulnerability to thyroid injury (Peeters, 2008) and declines in metabolism and excretion (Geller and Zenick, 2005). In addition, age-related neurocognitive decline may be hastened by exposure to POPs (Fitzgerald et al., 2008; Fitzgerald et al., 2012), and it is possible that thyroid hormones play an important role in that process (Liappas et al., 2009). A more focused evaluation of POP exposure, thyroid binding proteins, tissue deiodinase expression and thyroid hormones in an aging population is necessary to elucidate the findings of the current study. In conclusion, long-term exposure to POPs appears to elicit sex-specific impacts on thyroid hormones among aging residents of upper Hudson River communities. Further investigation is needed to more definitively explore the potential impact of these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Map of the study area: Hudson Falls, Fort Edwards and Glens Falls, New York.

Table 1

Distributions for demographic and clinical factors among 114 women and men residing in upper Hudson River communities.

Factor	Value	n	Mean	SD	Min.	Median	Max.
Age	Years	114	63.2	6.2	55	62.0	74
Sex	Female	48	42.1%	-	-	-	-
	Male	66	57.9%	-	-	-	-
BMI	kg/m ²	114	28.8	5.7	17.2	27.4	49.6
Alcohol	No	20	17.5%	-			
	Yes	94	82.5%	-			
	# of annual drinks ^a	94	320.2	372.7	1.0	208.0	2184.0
Cigarettes	No	98	86.0%	-	-	-	-
	Yes	16	14.0%	-	-	-	-
	# of annual packs ^b		296.8	244.1	0.7	273.8	730.0
Year enrolled	1	31	27.2%	-	-	-	-
	2	43	37.7%	-	-	-	-
	3	40	35.1%	-	-	-	-
Education	8th grade	5	4.4%	-	-	-	-
	9-12th grade	40	35.1%	-	-	-	-
	13-16 years	49	43.0%	-	-	-	-
	>16 years	20	17.5%	-	-	-	-
	Years	114	13.9	2.8	6	14.0	20
Income	\$0-\$15,000	5	4.6%	-	-	-	-
	\$15,001-\$30,000	21	19.4%	-	-	-	-
	\$30,001-\$45,000	26	24.1%	-	-	-	-
	\$45,001-\$60,000	24	22.2%	-	-	-	-
	\$60,001-\$75,000	29	17.6%	-	-	-	-
	\$75,001+	13	12.0%	-	-	-	-
Hx. thyroid disorder	No	112	98.3%	-	-	-	-
	Yes	2	1.8%	-	-	-	-

BMI, body mass index; Max., maximum observed value; Min., minimum observed value; SD, standard deviation.

^aAlcohol drinkers only;

^bCigarette smokers only

Table 2

Distributions for thyroid biomarkers, lipid measures and POP sums among women and men residing in upper Hudson River communities.

	Mean	SD	Min.	Median	Max.
Women (n=48):					
Thyroid biomarkers					
TSH (μIU/mL)	3.00	1.87	0.45	2.54	9.05
fT ₄ (ng/dL)	1.20	0.17	0.86	1.20	1.52
T ₄ (μg/dL)	8.67	1.46	6.16	8.63	12.05
T ₃ (ng/dL)	122.23	15.96	82.70	121.20	172.40
Total lipids (mg/dL) ^a	699.69	139.55	388.24	670.65	1105.08
POPs (μg/L serum)					
ΣPCB ₁ ^b	3.03	1.22	0.90	2.98	5.82
ΣPCB ₂ ^{b, *}	0.76	0.45	0.13	0.71	2.08
ΣPCB ₃ ^b	0.46	0.28	0.08	0.45	1.29
ΣPCB ₄ ^b	0.62	0.26	0.16	0.61	1.17
ΣDDT	3.59	2.99	0.02	2.76	13.82
ΣBDE	0.72	1.68	0.04	0.19	9.80
Men (n=66):					
Thyroid biomarkers					
TSH (μIU/mL)	2.62	1.84	0.23	2.12	14.78
fT ₄ (ng/dL)	1.25	0.17	0.79	1.27	1.68
T ₄ (μg/dL)	8.63	1.45	5.57	8.66	12.08
T ₃ (ng/dL)	125.96	17.95	90.75	125.65	189.00
Total lipids (mg/dL) ^a	666.18	109.43	411.59	670.65	1019.58
POPs (μg/L serum)					
ΣPCB ₁ ^b	3.34	1.90	0.82	2.93	11.93
ΣPCB ₂ ^{b, *}	0.65	0.63	0.00	0.52	3.67
ΣPCB ₃ ^b	0.41	0.34	0.00	0.34	2.02
ΣPCB ₄ ^b	0.74	0.51	0.09	0.65	3.35
ΣDDT	4.50	4.14	0.04	3.34	22.30
ΣBDE	0.42	0.75	0.04	0.16	4.74

DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; fT₄, free thyroxine; POP, persistent organic pollutant; SD, standard deviation; ΣPCB₁, sum of 39 PCB congeners; ΣPCB₂, sum of 12 PCB congeners with purported thyroid activity; ΣPCB₃, sum of 12 anti-estrogenic ('dioxin-like') PCB congeners; ΣPCB₄, sum of 7 estrogenic PCB congeners; ΣDDT, sum of p, p'- DDT and p, p'- DDE; ΣBDE, sum of 9 PBDE congeners; T₄, total thyroxine; T₃, total triiodothyronine; TSH, thyroid stimulating hormone.

^aEstimated as 2.27*cholesterol + triglycerides + 0.623 (Phillips et al., 1989);

^bn=4 missing values;

*P<0.05 for difference between women and men by Mann-Whitney U-test.

Table 3

Covariate-adjusted differences in serum thyroid hormones associated with doublings in POPs (μg/L serum) among 48 women residing in upper Hudson River communities.

Model (n) ^a	Difference	95% CI Low	95% CI High	P-value
TSH (μIU/mL):				
ΣPCB ₁ ^b	-0.76	-1.35	0.11	0.08
ΣPCB ₂ ^b	-0.51	-1.34	0.91	0.41
ΣPCB ₃ ^b	-0.93	-1.75	0.78	0.22
ΣPCB ₄ ^b	-0.87	-1.75	0.99	0.27
ΣDDT ^c	0.20	-0.08	0.52	0.16
ΣBDE ^d	-0.12	-0.33	0.11	0.27
fT ₄ (ng/dL):				
ΣPCB ₁	0.06	-0.06	0.17	0.35
ΣPCB ₂	0.07	-0.08	0.22	0.39
ΣPCB ₃	0.07	-0.14	0.28	0.52
ΣPCB ₄	0.04	-0.17	0.26	0.69
ΣDDT	-2.0 × 10 ⁻⁵	-0.04	0.03	1.00
ΣBDE	0.01	-0.01	0.04	0.33
T ₄ (μg/dL):				
ΣPCB ₁	0.76	-0.19	1.70	0.12
ΣPCB ₂	0.99	-0.22	2.20	0.11
ΣPCB ₃	1.01	-0.69	2.71	0.24
ΣPCB ₄	0.80	-0.97	2.57	0.37
ΣDDT	0.34	0.01	0.66	0.04
ΣBDE	0.20	-0.001	0.41	0.05
T ₃ (μg/dL):				
ΣPCB ₁	4.96	-5.44	15.36	0.35
ΣPCB ₂	-1.02	-13.96	11.93	0.88
ΣPCB ₃	0.09	-18.47	18.66	0.99
ΣPCB ₄	19.04	-2.05	40.13	0.08
ΣDDT	2.78	0.04	5.52	0.05
ΣBDE	2.15	-0.08	4.39	0.06

NOTE: P<0.05 in bold.

CI, confidence interval; DDE, p, p'-dichlorodiphenyldichloroethylene; DDT, p, p'-dichlorodiphenyltrichloroethane; fT₄, free thyroxine; POP, persistent organic pollutant; ΣPCB₁, sum of 39 polychlorinated biphenyl (PCB) congeners; ΣPCB₂, sum of 12 PCB congeners with purported thyroid activity; ΣPCB₃, sum of 12 anti-estrogenic ('dioxin-like') PCB congeners; ΣPCB₄, sum of 7 estrogenic PCB congeners; ΣDDT, sum of DDT and DDE; ΣBDE, sum of 9 polybrominated diphenyl ether congeners; T₃, total triiodothyronine; T₄, total thyroxine; TSH, thyroid stimulating hormone.

^aEach model adjusted for participant age (years), cigarette smoking (packs smoked in past year), alcohol consumption (drinks consumed in past year), education (years) and serum total lipids (mg/dL);

^b_{n=1} influential observation excluded;

^c_{n=2} influential observations excluded;

^d_{n=42} non-smokers.

Table 4

Covariate-adjusted differences in serum thyroid hormones associated with doublings in POPs ($\mu\text{g/L}$ serum) among 66 men residing in upper Hudson River communities.

Model ^a	Difference	95% CI Low	95% CI High	P-value
TSH ($\mu\text{IU/mL}$):				
ΣPCB_1 ^b	0.38	-0.16	1.07	0.18
ΣPCB_2 ^b	0.53	-0.21	1.53	0.18
ΣPCB_3 ^b	0.23	-0.62	1.51	0.64
ΣPCB_4 ^b	0.32	-0.44	1.41	0.46
ΣDDT ^b	0.16	-0.02	0.35	0.09
ΣBDE ^b	0.08	-0.08	0.25	0.33
fT ₄ (ng/dL):				
ΣPCB_1	-0.04	-0.13	0.04	0.30
ΣPCB_2	-0.08	-0.19	0.03	0.16
ΣPCB_3	-0.07	-0.22	0.08	0.36
ΣPCB_4	-0.05	-0.18	0.07	0.41
ΣDDT	-0.02	-0.04	0.01	0.28
ΣBDE	-0.03	-0.06	-0.01	0.01
T ₄ ($\mu\text{g/dL}$):				
ΣPCB_1	-0.15	-0.81	0.50	0.65
ΣPCB_2	-0.54	-1.43	0.36	0.24
ΣPCB_3	-0.58	-1.78	0.62	0.34
ΣPCB_4	-0.23	-1.25	0.78	0.65
ΣDDT	-0.05	-0.28	0.20	0.78
ΣBDE	-0.19	-0.40	0.01	0.07
T ₃ (ng/dL):				
ΣPCB_1	-2.85	-11.41	5.74	0.52
ΣPCB_2 ^b	-11.74	-24.93	1.44	0.08
ΣPCB_3 ^b	-15.54	-32.78	1.69	0.08
ΣPCB_4 ^c	-19.82	-32.69	-6.95	0.003
ΣDDT	-0.62	-3.60	2.36	0.68
ΣBDE	-0.72	-3.48	2.04	0.60

NOTE: P<0.05 in bold.

CI, confidence interval; DDE, p, p'-dichlorodiphenyldichloroethylene; DDT, p, p'-dichlorodiphenyltrichloroethane; fT₄, free thyroxine; POP, persistent organic pollutant; ΣPCB_1 , sum of 39 polychlorinated biphenyl (PCB) congeners; ΣPCB_2 , sum of 12 PCB congeners with purported thyroid activity; ΣPCB_3 , sum of 12 anti-estrogenic ('dioxin-like') PCB congeners; ΣPCB_4 , sum of 7 estrogenic PCB congeners; ΣDDT , sum of DDT and DDE; ΣBDE , sum of 9 polybrominated diphenyl ether congeners; T₃, total triiodothyronine; T₄, total thyroxine; TSH, thyroid stimulating hormone.

^a Each model adjusted for participant age (years), cigarette smoking (packs smoked in past year), alcohol consumption (drinks consumed in past year), education (years) and serum total lipids (mg/dL);

^b_{n=1} influential observation excluded;

^c_{n=2} observations excluded.

Table 5

Covariate-adjusted differences in serum thyroid hormones associated with concurrent doublings in PBDEs and PCBs or DDTs ($\mu\text{g/L}$ serum) among women and men residing in upper Hudson River communities.

Model (n) ^a	Women (n=48)		Men (n=66)	
	Difference ^b	P-value ^c	Difference ^b	P-value ^c
TSH ($\mu\text{IU/mL}$):				
$\Sigma\text{BDE} \times \Sigma\text{PCB}_1$	-1.03 ^d	0.46	-0.09 ⁱ	0.30
$\Sigma\text{BDE} \times \Sigma\text{PCB}_2$	-0.52 ^d	0.97	0.14 ⁱ	0.66
$\Sigma\text{BDE} \times \Sigma\text{PCB}_3$	-1.46 ^d	0.67	0.53 ^g	0.95
$\Sigma\text{BDE} \times \Sigma\text{PCB}_4$	-0.77 ^e	0.97	-0.26 ^e	0.19
$\Sigma\text{BDE} \times \Sigma\text{DDT}$	0.20 ^e	0.92	-0.01 ^e	0.44
fT ₄ (ng/dL):				
$\Sigma\text{BDE} \times \Sigma\text{PCB}_1$	0.16	0.08	-0.03	0.48
$\Sigma\text{BDE} \times \Sigma\text{PCB}_2$	0.18	0.38	0.02	0.14
$\Sigma\text{BDE} \times \Sigma\text{PCB}_3$	0.23	0.36	0.03	0.29
$\Sigma\text{BDE} \times \Sigma\text{PCB}_4$	0.26	0.25	0.05	0.15
$\Sigma\text{BDE} \times \Sigma\text{DDT}$	0.03	0.39	-0.03	0.60
T ₄ ($\mu\text{g/dL}$):				
$\Sigma\text{BDE} \times \Sigma\text{PCB}_1$	1.44	0.24	-0.19	0.91
$\Sigma\text{BDE} \times \Sigma\text{PCB}_2$	1.43	0.70	-0.78 ^d	0.95
$\Sigma\text{BDE} \times \Sigma\text{PCB}_3$	-0.19 ^d	0.67	-1.13 ^d	0.93
$\Sigma\text{BDE} \times \Sigma\text{PCB}_4$	1.79	0.58	0.29	0.39
$\Sigma\text{BDE} \times \Sigma\text{DDT}$	0.37 ^d	0.39	-0.24	0.68
T ₃ (ng/dL):				
$\Sigma\text{BDE} \times \Sigma\text{PCB}_1$	24.52 ^f	0.001	-12.44 ⁱ	0.90
$\Sigma\text{BDE} \times \Sigma\text{PCB}_2$	31.58 ^g	0.02	-19.65 ^d	0.65
$\Sigma\text{BDE} \times \Sigma\text{PCB}_3$	80.24 ^h	<0.0001	-49.84 ^e	0.30
$\Sigma\text{BDE} \times \Sigma\text{PCB}_4$	52.27 ^f	0.04	-9.64 ^e	0.42
$\Sigma\text{BDE} \times \Sigma\text{DDT}$	5.94 ^d	0.34	-0.15	0.57

NOTE: P<0.05 in bold.

CI, confidence interval; DDE, p, p'-dichlorodiphenyldichloroethylene; DDT, p, p'-dichlorodiphenyltrichloroethane; fT₄, free thyroxine; ΣPCB_1 , sum of 39 PCB congeners; ΣPCB_2 , sum of 12 PCB congeners with purported thyroid activity; ΣPCB_3 , sum of 12 anti-estrogenic ('dioxin-like') PCB congeners; ΣPCB_4 , sum of 7 estrogenic PCB congeners; ΣDDT , sum of DDT and DDE; ΣBDE , sum of 9 PBDE congeners; T₃, total triiodothyronine; T₄, total thyroxine; TSH, thyroid stimulating hormone.

^aEach model adjusted for participant age (years), cigarette smoking (packs smoked in past year), alcohol consumption (drinks consumed in past year), education (years) and serum total lipids (mg/dL);

^boverall effect for a doubling in concentrations of POP sums from model with $\Sigma\text{PCB}_{1-4} + \Sigma\text{BDE} + \Sigma\text{PCB}_{1-4} \times \Sigma\text{BDE}$ or $\Sigma\text{DDT} + \Sigma\text{BDE} + \Sigma\text{DDT} \times \Sigma\text{BDE}$;

^cP-value for the $\Sigma\text{PCB}_{1-4} \times \Sigma\text{BDE}$ or $\Sigma\text{DDT} \times \Sigma\text{BDE}$ interaction term;

d _{n=1} influential observation excluded;

e _{n=2} influential observations excluded;

f _{n=42} non-smokers;

g _{n=4} influential observations excluded;

h _{n=5} influential observations excluded;

i _{n=3} influential observations excluded.

Table 6

Covariate-adjusted differences in serum thyroid hormones associated with concurrent doublings in DDTs and PCBs ($\mu\text{g/L}$ serum) among women and men residing in upper Hudson River communities.

Model (n) ^a	Women (n=48)		Men (n=66)	
	Difference ^b	P-value ^c	Difference ^b	P-value ^c
TSH ($\mu\text{IU/mL}$):				
$\Sigma\text{DDT} \times \Sigma\text{PCB}_1$	-0.72 ^d	0.93	0.35 ^d	0.82
$\Sigma\text{DDT} \times \Sigma\text{PCB}_2$	-0.51 ^e	0.51	0.89 ^d	0.42
$\Sigma\text{DDT} \times \Sigma\text{PCB}_3$	-0.87 ^d	0.59	-0.14 ^d	0.90
$\Sigma\text{DDT} \times \Sigma\text{PCB}_4$	-0.93 ^e	0.57	0.10 ^d	0.71
fT ₄ (ng/dL):				
$\Sigma\text{DDT} \times \Sigma\text{PCB}_1$	0.01	0.03	-0.05	0.77
$\Sigma\text{DDT} \times \Sigma\text{PCB}_2$	0.10 ^d	0.49	-0.16	0.14
$\Sigma\text{DDT} \times \Sigma\text{PCB}_3$	0.02	0.07	-0.10	0.45
$\Sigma\text{DDT} \times \Sigma\text{PCB}_4$	0.001	0.07	-0.06	0.59
T ₄ ($\mu\text{g/dL}$):				
$\Sigma\text{DDT} \times \Sigma\text{PCB}_1$	0.18	0.01	-0.18	0.98
$\Sigma\text{DDT} \times \Sigma\text{PCB}_2$	0.55	0.03	-1.22	0.23
$\Sigma\text{DDT} \times \Sigma\text{PCB}_3$	0.31	0.01	-1.03	0.53
$\Sigma\text{DDT} \times \Sigma\text{PCB}_4$	-0.27	0.01	-0.43	0.76
T ₃ (ng/dL):				
$\Sigma\text{DDT} \times \Sigma\text{PCB}_1$	0.10 ^d	0.13	-11.88	0.10
$\Sigma\text{DDT} \times \Sigma\text{PCB}_2$	0.88 ^f	1.00	-13.40 ^d	0.81
$\Sigma\text{DDT} \times \Sigma\text{PCB}_3$	-3.71 ^e	0.12	-18.98 ^d	0.62
$\Sigma\text{DDT} \times \Sigma\text{PCB}_4$	-1.83 ^d	0.18	-18.02	0.04

NOTE: P<0.05 in bold.

CI, confidence interval; DDE, p,p'-dichlorodiphenyldichloroethylene; DDT, p, p'-dichlorodiphenyltrichloroethane; fT₄, free thyroxine; PCB, polychlorinated biphenyl; ΣPCB_1 , sum of 39 PCB congeners; ΣPCB_2 , sum of 12 PCB congeners with purported thyroid activity; ΣPCB_3 , sum of 12 anti-estrogenic ('dioxin-like') PCB congeners; ΣPCB_4 , sum of 7 estrogenic PCB congeners; ΣDDT , sum of DDT and DDE; T₃, total triiodothyronine; T₄, total thyroxine; TSH, thyroid stimulating hormone.

^a Each model adjusted for participant age (years), cigarette smoking (packs smoked in past year), alcohol consumption (drinks consumed in past year), education (years) and serum total lipids (mg/dL);

^b Overall effect for a doubling in concentrations of POP sums from model with $\Sigma\text{DDT} + \Sigma\text{PCB}_{1-4} + \Sigma\text{DDT} \times \Sigma\text{PCB}_{1-4}$;

^c P-value for the $\Sigma\text{DDT} \times \Sigma\text{PCB}_{1-4}$ interaction term;

^d n=1 influential observation excluded;

^e n=2 influential observations excluded;

^f n=3 influential observations excluded.