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Relationships of Thyroid Hormones with PCBs, Dioxins, Furans, and DDE in Adults

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Abbreviations:

AhR=aryl hydrocarbon receptor

BMI=body mass index

CDD=chlorodibenzo-p-dioxin

CDF=chlorodibenzofuran

CI=confidence interval

DDE=*p,p'*-diphenyldichloroethene

HPT=hypothalamo-pituitary-thyroid

LOD=limit of detection

NHANES=National Health and Nutrition Examination

NSAIDs=nonsteroidal anti inflammatory

PCBs=polychlorinated biphenyls

PCDDs=polychlorinated dibenzo-p-dioxins

PCDFs=polychlorinated dibenzofurans

T_3=triiodothyroxine

T_4=thyroxine

TEF=toxic equivalency factor

TEQs=toxic equivalents

TSH=thyroid stimulating hormone

Outline of manuscript section headers:

ABSTRACT

Background: Thyroid hormone homeostasis can be disrupted by exposure to ubiquitous and bioaccumulative organochlorines such as polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-p-dioxins (PCDDs). While investigations of health effects have generally focused on human populations with relatively high exposures through occupation, accident, or high fish consumption, general population exposures may also carry risk.

Methods: Associations of total thyroxine and thyroid stimulating hormone (TSH) with PCBs, dioxin-like toxic equivalents (TEQs), and *p,p'*-diphenyldichloroethene (DDE) were studied in adult participants without thyroid disease who participated in the 1999-2002 National Health and Nutrition Examination, a cross sectional survey examining a random sample representative of the US population.

Results: We found inverse associations of total thyroxine with exposure to TEQs, in both genders, with stronger associations in women. In women, mean thyroxine was 8.2 ug/dL, and levels were on average 0.75 ug/dL lower (95% confidence interval = 0.04, 1.46) in women in the highest quintile of TEQ exposure compared with the lowest 2 quintiles. Effects were stronger in people older than 60 years, with negative associations of thyroxine with PCBs and TEQs, and positive associations of TSH with PCBs and TEQs in older women, and a negative association of TSH with PCBs in older men.

Conclusions: The data show a dose-dependent decrease in total thyroxine with exposure to dioxin-like toxic equivalents at levels similar to those found in the general US population. The effects were stronger in women and suggest that older adults, who have a high risk of thyroid disease, may be more at risk for disruption of thyroid hormone homeostasis by dioxin-like organochlorines than younger adults.

INTRODUCTION

Polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and *p,p'*-diphenyldichloroethene (DDE) are widespread persistent environmental contaminants. Although human body burdens of these chemicals have been decreasing over time (Hagmar et al. 2006; Schecter et al. 2005), they remain detectable in most of the population due to their long half life in the body (Geyer et al. 2002) and continued exposure primarily through the food supply (Needham et al. 2005).

Organochlorines have been associated with a number of health effects, including disruption of thyroid hormone homeostasis. Thyroid hormones are under control of the hypothalamo-pituitary-thyroid (HPT) axis. Reduction of circulating thyroxine (T_4) is compensated for by release of thyroid stimulating hormone (TSH) from the pituitary, which in turn stimulates the thyroid to produce more hormones. In animals, PCBs and dioxin-like compounds disrupt the HPT axis, decreasing thyroxine levels, with inconsistent changes in TSH (Brouwer et al. 1990; Fisher et al. 2006; van Birgelen et al. 1992, 1995). Dioxin-like chemicals are thought to accomplish this through binding to the aryl hydrocarbon receptor (AhR), which induces uridine diphosphate glucuronosyltransferase enzymes, leading to increased glucuronidation and excretion of thyroxine (Fisher et al. 2006; van Birgelen et al. 1995). Ortho substituted PCBs, which do not bind to the AhR, disrupt the HPT axis through other mechanisms which may include increased glucuronidation through non AhR pathways, displacement of thyroxine from the binding protein transthyretin, and direct effects on TSH release from the pituitary (Brouwer et al. 1990; Khan et al. 2002; van Birgelen et al. 1992, 1995).

The effects of organochlorines on thyroid hormone homeostasis have been studied in humans, but results have not been consistent. Most investigations of endocrine disruption by PCBs, PCDDs, PCDFs and DDE in humans have focused on populations with higher exposures, through occupation or residence near areas contaminated by industry (Calvert et al. 1999; Langer et al. 1998, 2004; Osius et al. 1999; Ott et al. 1994; Pavuk et al. 2003; Persky et al. 2002; Schell et al. 2004; Triebig et al. 1998), accident (Murai et al. 1987), or fish consumption (Hagmar et al. 2001a, 2001b; Langer et al. 2007; Persky et al. 2001; Rylander et al. 2006; Turyk et al. 2006a). General population exposures have also been associated with thyroid disruption (Meeker et al. 2007; Takser et al. 2005), although studies have not usually been population based. There may be a number of factors related to the

inconsistent human findings, including different detection methods for biomarkers and endogenous hormones, varying overall exposure levels and concomitant chemical exposures, as well as differences in age, gender, nutritional status, comorbidities, and medication use.

In this study, we examined the effects of low-level general population organochlorine exposures on endogenous thyroid hormones in a population without reported thyroid disease. The National Health and Nutrition Examination (NHANES) is a cross sectional survey examining a random sample representative of the US population (CDC 2007). During the 1999-2000 and 2001-2002 survey rounds, PCB, PCDD, and PCDF congeners, DDE, total thyroxine and TSH were measured in approximately one-third of the NHANES sample. Data on individual organochlorine congeners have been presented in the Third National Report on Human Exposure to Environmental Chemicals (CDC 2005) and by Needham et al. (2005). This paper focuses on the cross sectional relationships of PCB, TEQ, and DDE body burdens with thyroxine and TSH serum levels in these two NHANES samples.

METHODS

Participants

Data from NHANES survey cycles conducted in 1999-2000 and 2001-2002 were obtained from the publicly accessible internet site (CDC 2007). During these 2 data collection cycles, total T_4, TSH, DDE, and PCB, PCDD, and PCDF congeners were measured in serum sampled from one third of the participants. This subsample is also a nationally representative sample of the US population (CDC 2007). Participants under age 20 were not tested for PCDD and PCDF congener data during the 2001-2002 cycle, and as a result they were excluded from the analysis. After exclusion of participants without both organochlorine and thyroid hormone measurements or with current thyroid disease or thyroid medication use (n=150 total: 36 men and 114 women), a total of 995 participants for the 1999-2000 cycle and 1450 participants for the 2001-2 cycle were available for analysis of the associations of thyroid hormones with organochlorine body burdens. We were not able to examine associations of diagnosed hypothyroidism with organochlorines because the survey questions relating to thyroid conditions did not distinguish between different types of thyroid diseases.

Thyroid Hormones

Total thyroxine (ug/dL) and TSH (IU/L) were measured in serum by two different laboratories. Sera collected during the 1999-2000 cycle and part of the 2001-2002 cycle were measured by the Coulston Foundation (Alamogordo, NM), while the remainders of samples from the 2001-2002 cycle were tested at Collaborative Laboratory Services (Ottumwa, IA). The National Center for Health Statistics evaluated the 2001-2002 TSH and thyroxine data sets from the 2 laboratories and determined that the variables were comparable across the two years (Blount et al. 2006). Total T_4 was measured on the Hitachi 704 chemistry analyzer (Coulson Foundation) and by a paramagnetic particle, chemiluminescent, competitive binding enzyme immunoassay (Collaborative Laboratory Services). TSH was measure by an IMx ultrasensitive hTSH II microparticle enzyme immunoassay (Coulson Foundation) and by a two-site, paramagnetic particle and chemiluminescent immunoassay (Collaborative Laboratory Services). Both laboratories reported a reference range of 5.4-12.8 ug/dL for total T_4. Reference ranges for TSH were 0.47-5.0 IU/L at the Coulson Foundation and 0.24-5.4 at the Collaborative Laboratory Services.

PCBs, dioxins, furans, and DDE Measurements

Organochlorines were measured in serum by high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry at the Organic Toxicology Branch, National Center for Environmental Health, CDC. We created a variable for total PCBs by summing individual PCB congeners. TEQs were calculated for each dioxin, furan, coplanar PCB and mono-ortho PCB congener by multiplying the toxic equivalency factor (TEF) by the congener concentration in pg/g (Van den Berg et al. 2006) and then summing the values to calculate total TEQs. For congeners with results below the limit of detection (LOD), the CDC imputed the value for the congener as the LOD for that specific congener divided by the square root of 2. The LOD varied for each participant, as it was dependent on the volume of the sample submitted for analysis. In the first sampling cycle (1999-2000), fewer congeners were measured and more individual results were below the LOD, compared with the second cycle (Table 1). Only congeners that had greater than 10% of results above the LOD were included in the PCB and TEQ sums; therefore the specific congeners in the PCB and TEQ sums differed in the two sampling cycles (Table 1). When results for more than 1 congener were not reported by the CDC for a participant, the participant was coded as missing for total PCBs or TEQs.

Covariates

We considered medications that can alter hormone homeostasis (Meier and Burger 2005) to be potential effect modifiers or confounders of the associations of organochlorines on thyroid hormones. Medications were identified in the prescription drug medication and the analgesics/pain reliever questionnaires, and included estrogens and/or progesterone, other steroid hormones (androgens, adrenal corticosteroids, tamoxifen, raloxifene, and pituitary hormones), nonsteroidal anti inflammatory (NSAIDs), furosemide, beta-blockers, blood glucose regulators, and other medications thought to affect thyroid hormones (amidoarone, carbamazepine, chlorpropamide, carbidopa/levodopa, heparin, interferon, lithium, phenytoin, phenobarbital, and sulfasalazine). Because estrogen alters total thyroxine binding concentrations, we also considered current pregnancy and menopausal status to be potential confounders or effect modifiers. Smoking can affect thyroid hormone levels through the metabolism of cyanide in smoke to thiocyanate, a potent inhibitor of iodide transport (Meier and Burger 2005). We used serum cotinine levels to estimate tobacco smoke exposure (Organic Analytical Toxicants Branch, National Center for Environmental Health, CDC). Serum lipids are generally associated with serum organochlorine concentrations because of partitioning and they also often increase in hypothyroidism. Total serum lipids were calculated by the formula given in the NHANES laboratory manual for dioxins: total cholesterol (mg/dl)*2.27 + triglycerides (mg/dl) + 62.3 (CDC 2007). Age (years), gender, race (Mexican American, African American, Caucasian, or other) and body mass index (BMI) were also included as covariates. BMI was calculated from height and weight measured during the NHANES examination (weight in kg/height in m^2). For 85 of the 91 participants who were missing measured BMI, we imputed BMI using self reported weight and height. In participants with both measures, the correlation between self reported and measured BMI was greater than r=0.9.

Statistical Analyses

NHANES uses a complex sampling design requiring the use of sample weights to adjust for the unequal probability of selection into the survey and to adjust for the possible bias resulting from nonresponse; weights are post-stratified to US Census Bureau estimates of the US population. Data management and analyses were performed with SAS 9.1 (Cary, NC), using sample weights for the individual 2 year cycles or 4 year combined cycles, as appropriate, and calculating variances that accounted for the complex survey design.

Because the data were not normally distributed, natural log transformations of TSH, total PCBs, total TEQs, DDE, BMI, and cotinine were used for analysis. For univariate analyses, means were calculated with SAS PROC SURVEYMEANS, using the domain command to estimate means in subpopulations, and differences between groups were assessed with SAS PROC SURVEYREG. Categorical data was evaluated with SAS PROC SURVEYFREQ and differences between groups were tested using SAS PROC SURVEYLOGISTIC.

Associations of thyroid hormones with PCB, TEQs and DDE were modeled using PROC SURVEYREG. SAS does not allow for subpopulation analyses in PROC SURVEYREG, therefore we used Stata 6.0 (StataCorp LP, College Station, TX) to calculate the variances for the subpopulation models. Stata (StataCorp) uses a variance estimator that accurately measures the sample to sample variability of the subpopulation estimates for the survey design used to collect the data (StataCorp 2005). Because summed PCBs and TEQs were significantly higher in the second sampling cycle (Tables 1 and 2), associations were tested for each sampling cycle individually, using continuous predictor variables. We could not directly combine sampling cycles for analysis because fewer congeners were summed and more individual results were below the LOD in the first sampling cycle (Table 1). In order to combine data from both cycles for analysis, we assumed that the true exposure levels of the US population did not change substantially between 1999-2000 and 2001-2002, and, therefore, that the ranks of the exposure measurements for each cycle should be comparable. However, ranking should be more valid for ordering participants with high rather than low exposures, since most of the total PCB and TEQ sums that were composed of a large proportion of congeners below the LOD fell into the lower ranks. Thus, data from both sampling cycles were combined by ranking the PCB, TEQ, and DDE levels into quintiles separately for each cycle, merging the data from both cycles, and pooling the lowest 2 quintiles. Dose response models were estimated using indicator variables for quintiles 3, 4 and 5, with quintiles 1 and 2 combined as the reference category, or the ordinal variable (quintile 1-2, 3, 4, 5), to test for a trend over the categories. For these analyses we used wet weight PCB, PCDD, and PCDF congeners, rather than lipid-standardized measurements and included serum lipids as a covariate (Schisterman et al. 2005).

Organochlorines and thyroid hormones were associated with age and with many of the potential covariates we identified prior to the analysis. We therefore evaluated relationships of the covariates with exposure and outcome

variables after controlling for age. TSH was negatively associated with cotinine and postmenopausal status, and positively associated with BMI and use of other medications ($p<0.05$). Thyroxine was negatively associated with lipids, cotinine, and furosamide use, and positively associated with estrogen/progesterone use and pregnancy ($p<0.05$). At least one exposure was positively associated ($p<0.05$) with lipids, BMI, diabetes medication use, estrogen/progesterone use, beta blocker use, and postmenopausal status, and negatively associated with steroid hormone use, other medication use, and serum cotinine. Regression models were individually adjusted for serum lipids, age, log BMI, gender, race, log cotinine and use of NSAIDs, furosemide, beta-blockers, blood glucose regulators, other medications, and, for women, completion of menopause. Analyses of the combined study cycles were also adjusted for cycle. Participants taking estrogen and/or progesterone (n=201), other steroid hormones (n=70 total, n=40 women, n=30 men), and pregnant participants (n=163) were excluded from the analyses because potential modification of the effects of organochlorines on thyroid hormones by estrogen and/or progesterone medications was noted in stratified analyses.

RESULTS

Demographic information, medication use, and thyroid hormone levels for participants without thyroid disease are shown in Table 3. Total T_4 was higher in women than men, but TSH did not differ by gender (Table 3). T_4 was higher and TSH was lower in the 2001-2002 than the 1999-2000 cycle ($p<0.05$, not shown). BMI, lipids, TSH, percent with TSH above 5.0 IU/L, and use of medications (estrogens and/or progesterones, other steroid hormones, beta blockers, NSAIDs, and blood glucose regulators) increased with age, while cotinine exposure decreased with age ($p<0.05$, not shown).

Total PCBs, total TEQs and DDE were positively associated with age in men and women ($p<0.05$, not shown), but mean levels did not differ significantly by gender ($p>0.05$, not shown). Correlations among organochlorines were positive, with the strongest associations between PCBs and TEQs (range: $r=0.44$ to 0.82). The main congeners contributing to the sum of PCBs were 138, 153, and 180, which comprised 54% and 41% of the total PCBs in the first and second cycles, respectively, with these individual congeners highly correlated with sum PCBs ($r=0.90$ to 0.99). Approximately 76% of total TEQs were from the congeners 1,2,3,7,8-PentaCDD, 1,2,3,6,7,8-HexaCDD, 2,3,4,7,8-PentaCDF, and PCB 126 in cycle 1 and from these 4 congeners plus 2,3,7,8-TetraCDD in cycle

2. TEQs for these congeners were significantly associated with total TEQs (r=0.71 to 0.89), with stronger associations in the second cycle than the first cycle. Since both total PCBs and total TEQs were higher in the second cycle than in the first cycle (Table 2), we first modeled the relationships of these organochlorines with thyroid hormones separately for each sampling cycle (Tables 4 and 5).

Total thyroxine was negatively associated with total TEQs in men and women, with stronger associations of thyroxine with TEQs for both men and women in the second sampling cycle than the first cycle (Tables 4 and 5). Results, however, were statistically significant only in older women and men, and in older men the results were inconsistent and were statistically significant only in the second cycle with further adjustment for PCB and DDE levels. In women, TSH was positively associated with TEQs, with a statistically significant association only in older women in the second sampling cycle. In men, associations of TSH with TEQs were generally negative, but not significant.

Associations of PCBs with thyroxine and TSH were inconsistent in women. In older women, PCBs were negatively associated with thyroxine and positively associated with TSH, with statistically significant associations only in the second cycle (Table 4). In men, TSH was negatively associated with PCBs, with statistically significant associations in older men during the first cycle and during the second cycle with further adjustment for TEQs and DDE. Associations of thyroxine with PCBs in men were inconsistent and were not statistically significance (Table 5).

Thyroxine was positively associated with DDE in all women and in younger women, with a statistically significant association only in the first cycle in younger women. In older women the direction of the association differed by cycle (Table 4). In men, thyroxine was negatively, but not significantly, associated with DDE, and again the direction of the association differed in older participants (Table 5). Associations of TSH with DDE were inconsistent and not significant.

Data from both sampling cycles were combined by ranking the exposure measurements into quintiles for each individual cycle, merging the data from both cycles, and combining the lowest 2 quintiles. A dose response for the associations of total TEQs with thyroxine were found for women and men, with a significant trend for the dose only for women (Figure 1). The decrease in total thyroxine with an increase in one quintile of total TEQs was 0.25 ug/dL (95% confidence interval=0.02, 0.48) for women. The thyroxine decrease was 0.75 ug/dL (95% confidence

interval=0.04, 1.46) for women in the highest compared with the lowest TEQ quintile. The association for women remained significant or of borderline significance with further adjustment for quintile total PCBs or quintile DDE. No other significant associations were found for the combined data cycles for thyroxine with PCBs or DDE or for TSH with any exposure in either men or women.

The analyses were repeated using a different method to calculate PCBs and TEQs. Only congeners detectable in more than 50% of participants were included in the sums for PCBs and TEQs (Table 1). Results were generally similar for the analyses of data from the individual cycles, except thyroxine was not significantly associated with TEQs in older women in the first cycle, and thyroxine became significantly associated with TEQs in older men in the second cycle (not shown). In the combined cycle analysis the association of TEQs with thyroxine in women was slightly weaker and in men was slightly stronger ($0.05<p<0.15$ for both, not shown). In older men, the association of PCBs with TSH in the first cycle did not remain significant (not shown).

Because this data is a sample from the general population, we would expect that some participants might have unusually high contaminant exposures due to high sport fish consumption or occupation and abnormal thyroid hormone levels because of undiagnosed thyroid disease. In order to determine if model results were affected by extreme values, we excluded participants with exposure values more than 3 interquartile ranges above the 75th percentile (PCBs>7 ng/g, n=25, TEQs>0.62 pg/g, n=20, DDE >30 ng/g, n=78), as well as participants with very high TSH (42.7, 44.0, 81.9, 234.6 IU/L) and thyroxine levels (27 ug/dL). Significant relationships between thyroid hormones and TEQs remained. For men over 60 the negative association of PCBs with TSH became significant in the second sampling cycle, but did not remain significant in the first sampling cycle, and for women over 60 in the second sampling cycle the positive association of PCBs with TSH did not remain significant (not shown).

DISCUSSION

In the adult participants of the National Health and Nutrition Examination from 1999-2002, total thyroxine was negatively associated with serum dioxin-like TEQs in a dose dependent fashion, with stronger associations in women than men. Associations of organochlorines with thyroid hormones were stronger in participants over 60 years of age, with lower thyroxine and higher TSH with both PCB and TEQ exposure in women, and lower TSH with PCB

exposure in men. With further adjustment for multiple exposures, the negative associations of thyroxine with TEQs generally remained significant or borderline significant.

Overall, results of human studies on the effects of PCBs, dioxins and DDE on thyroid hormones have been inconsistent. However, a variety of factors may be related to the inconsistent findings, the most important of which may include small numbers of participants, varying overall exposure levels, use of various detection methods for biomarkers and endogenous hormones, and differing age, gender, and unmeasured exposures to chemicals affecting hormone homeostasis.

In three studies with high exposures, dioxin like chemicals have been associated with increased thyroid hormones. Occupational exposures to dioxin-like compounds were associated with increased levels of free thyroxine (mean 220 pg/g lipid TEQ; Calvert et al. 1999), as well as total T_4 and thyroid binding globulin (range <1 to 533 pg/g lipid; Ott et al. 1994). Exposure to PCBs and furans in the Yusho outbreak was associated with increased total T_3 and T_4, but not TSH, 16 years after exposure (mean 222.4 pg/g lipid 30 years after exposure, Murai et al. 1987; Nagayama et al. 2001). Results have varied more for lower exposures, with no association with total thyroxine or TSH in metal recyclers (mean 42 pg/g lipid; Treibig et al. 1998), increased TSH, but no change in total T_4 in Vietnam veterans (mean 45.7 pg/g lipid, Pavuk et al. 2003), decreased TSH, but no association with total T_3, total T_4 or free T_4 in male fish consumers (range 11-105 pg/g lipid; Turyk et al. 2006a), and decreased total T_3 and total T_4, but no change in TSH and free T_4 in pregnant women (mean 74.9 pg/g lipid in breast milk; Koopman-Esseboom et al. 1994). The differential effects of dioxins on thyroid hormone homeostasis that appear to be related to exposure levels could potentially be attributed to down regulation of the Ah receptor after large exposures, such as recently noted after the Seveso accident (Landi et al. 2003). In the current study, with an average TEQ exposure of 12-18 pg/g lipid, we observed decreased thyroxine with dioxin-like exposure, in agreement with the Koopman-Esseboom study (1994).

Most studies of exposure to PCBs have found inverse associations with thyroxine. A negative association with one or more thyroid hormones and positive associations with TSH were found with measures of PCB exposure in children living near PCB-contaminated sites (Osius et al. 1999; Schell et al. 2004). PCB production workers and controls from a less polluted area had similar levels of total T_4 and TSH (Langer et al. 1998), but a later study of

adults from a heavily polluted area demonstrated positive relationships of PCBs with free T_4 and free T_3 (Langer et al. 2004). Male capacitor manufacturing employees with exposure to PCBs and chlorinated naphthalene had decreased TSH and no change in total thyroxine (Persky et al. 2002). In frequent fish consumers, an inverse association of PCB 153 was found with total T_3 among women (Hagmar et al. 2001b), but not men (Hagmar et al. 2001a; Rylander et al. 2006). In a group of frequent Great Lakes fish consumers, inverse associations of PCB levels with total thyroxine were found in men and women and with free T_4 in women (Persky et al. 2001), and in a different subgroup of participants from the same study, inverse associations of PCBs with total T_3, total T_4 and TSH in men were found (Turyk et al, 2006a). Much smaller effects of PCBs on thyroid hormones were noted in New York anglers and in a population in Spain (Bloom et al. 2003; Sala et al. 2001). Negative associations were found for total T_3 with PCBs in pregnant women and men with low level exposure (Meeker et al. 2007; Takser et al. 2005), but in the men only after control for DDE. In the current study we saw no effect of PCBs on thyroid hormones in the NHANES cohort as a whole, although we did find decreased thyroxine and increased TSH in older women and decreased TSH in older men. It is possible that there were effects on unmeasured thyroid hormones, such as free thyroxine or total T_3, or that levels of PCBs were too low to affect thyroid homeostasis.

Few investigations have examined associations of DDE with thyroid hormones. No associations were found for DDE with thyroid hormones in male or female fish consumers (Hagmar et al. 2001a; Persky et al. 2001; Turyk et al. 2006a), a positive association was found with TSH in male fish consumers (Rylander et al. 2006), a negative association was found for total T_3 in pregnant women with low levels of exposure (Takser et al. 2005), and positive associations were found with total T_3 and free T_4 in men with low exposure (Meeker et al. 2007). In this study, we did not find any significant associations of DDE with thyroid hormones when both sampling cycles were combined, although thyroxine was positively associated with DDE in younger women, but only in the first sampling cycle. In older participants, associations in the first and second cycles were inconsistent.

The hypothalamo-pituitary-thyroid axis normally responds to decreases in free thyroxine with increased production of TSH. In women over 60 years, we found that PCBs and TEQs were negatively associated with thyroxine and positively associated with TSH, consistent with a normal pituitary response to decreased thyroxine levels. Elevated TSH, even within the high normal reference range, may be a marker for increased risk of

hypothyroidism (Vanderpump 2005). In adults living in areas with sufficient iodide intake, the most common cause of hypothyroidism is autoimmune disease. Markers of autoimmune disease, such as anti-thyroperoxidase antibodies and thyroid hypoechogenicity, have been associated with PCB exposure (Langer et al. 2004, 2007). Our observation of decreased thyroxine and increased TSH in older women with higher exposure to dioxin-like TEQs or PCBs is intriguing since this population group has the highest risk of hypothyroidism, reaching an annual incidence rate of over 13/1000 in women 75-80 years of age (Vanderpump 2005). The NHANES dataset did not provide sufficient information on diagnosis of hypothyroidism to allow us to study the effects of organochlorine exposure on the prevalence of hypothyroidism. Overall, the decreases in thyroxine noted in this analysis may or may not be significant on an individual level, but could substantially contribute to disease burden in the population.

Associations of organochlorines with thyroid hormones in this study were stronger in females than males, similar to results in two studies of fish consumers (Hagmar et al. 2001a, 2001b; Persky et al. 2001), in children aged 7-10 years (Osius et al. 1999), and a study in infants (Wang et al. 2005). The stronger effects of organochlorines, particularly in older females, could be related to a number of age and/or gender associated factors, including hormonal environment, organochlorine exposure and metabolism, and risk of developing preclinical and clinical thyroid disease. In these NHANES participants, PCBs and dioxin-like congeners differed by gender, with females having greater levels of dioxin-like congeners than males (Needham et al. 2005), which may be related to differential metabolism or elimination influenced by body fat or hormonal factors (Geyer et al. 2002).

Levels of PCBs, TEQs, and DDE in the NHANES participants in the 2001-2 cycle were similar to those found in infrequent sport fish consumers (Turyk et al. 2006b), and to age-specific dioxin, furan, and coplanar PCB TEQs in various US populations (Patterson et al. 2004). PCBs and TEQs were significantly lower in participants during the 1999-2000 cycle than the 2001-2002 cycle, which limited our ability to draw conclusions about effects of these organochlorines on hormones in the first study cycle. Misclassification is more likely in the participants with lower levels of exposure due to the larger number of results below the LOD, caused in part by laboratory limitations related to small serum volumes (Needham et al. 2005). We examined data from both cycles simultaneously to increase our power to detect gender specific associations. To this end, we ranked both cycles into quintiles, merged them, and pooled the lowest 2 quintiles for analysis, and, although some residual misclassification may be present in

this analysis, the results for TEQs and thyroxine are consistent with those found in the analyses of the second cycle alone. The inconsistencies in associations of DDE with thyroid hormones cannot be explained by differences in exposure levels by study cycle. An additional source of measurement error could come from the change in the laboratory performing the hormone tests during the second cycle**,** although the CDC has determined that values for TSH and thyroxine are comparable across the second cycle (Blount et al. 2006). In addition, any misclassification of the hormone levels in the second cycle should be nondifferential with regard to exposure and thus would be more likely to weaken associations in the second cycle. In fact, we saw stronger organochlorine-hormone associations in the second compared with the first cycle.

The cross sectional study design limits our ability to evaluate the temporal association of organochlorine exposure with thyroid hormone changes, but generally concentrations of organochlorines reflect long term exposures with many congeners, particularly the more highly chlorinated congeners, persisting for years within the body (Geyer et al. 2002). We have adjusted for many biological factors that could influence the relationship between thyroid hormones and organochlorines, but thyroid hormones affect several aspects of metabolism, and there may be other factors that are related to both serum levels of organochlorines and thyroid hormones for which we have not controlled. Additional hormone measurements, such as triiodothyroxine, free thyroxine, and thyroid binding globulin, might have helped to elucidate mechanisms related to the associations we found between TEQs and thyroid hormones. In addition, the decreases in thyroxine could be associated with other unmeasured exposures, such as polybrominated biphenyl ethers or PCB metabolites, which are associated with the measured organochlorines. While our main findings generally remained significant or borderline significant after adjustment for other measured organochlorines, evaluation of the effects of multiple exposures can be imprecise due to strong associations among exposures. Finally, the results for the subpopulation analyses should be viewed with caution in consideration of the sample size, which may be too small to produce reliable estimates using population-based statistical methodology.

Despite these limitations and issues related to sample analysis for organochlorines and thyroid hormones described above, this study has a number of strengths including generally similar trends for results in both sampling cycles for the primary findings, large number of participants, population-based sampling design, and consistency with results of toxicological studies in animals. Despite the fact that decreases over time in PCBs and/or dioxins have

been noted in cross sectional and longitudinal studies (Hagmar et al. 2006; Schecter et al. 2005), the US population continues to be exposed to low levels of these persistent chemicals, primarily through a dietary route. The data show a dose-dependent decrease in total thyroxine with exposure to dioxin-like toxic equivalents, with an average decrease of 0.75 ug/dL, or 9% of average thyroxine levels, in the highest quintile compared with the lowest quintile in women, and suggests that older adults, who have a high risk of thyroid disease, may be more at risk for disruption of thyroid hormone homeostasis by organochlorines than younger adults.

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Table 1: Serum Organochlorines in 1999-2002 NHANES Participants without Thyroid Disease

Organochlorine	% of Participants with results below LOD:		Median Concentration (pg/g):	
	1999-2000 Cycle	2001-2002 Cycle	1999-2000 Cycle	2001-2002 Cycle
PCB 66[a]	NA[b]	89	-	NC[c]
PCB 74[a]	47	33	41	50
PCB 99[a]	59	38	NC	40
PCB 105[a]	86	79	NC	NC
PCB 118[a,d]	44	27	48	59
PCB 126[d]	36	12	0.12	0.16
PCB 138[a]	49	7	115	164
PCB 146[a]	66	53	NC	NC
PCB 153[a]	42	4	200	234
PCB 156[a,d]	58	46	NC	34
PCB 169[d]	36	12	0.09	0.13
PCB 170[a]	44	25	62	74
PCB 172[a]	NA	84	-	NC
PCB 177[a]	NA	83	-	NC
PCB 178[a]	87	81	NC	NC
PCB 180[a]	38	11	152	180
PCB 183[a]	80	70	NC	NC
PCB 187[a]	43	34	45	51
PCB 194[a]	NA	39	-	46
PCB 196[a]	NA	46	-	34
PCB 201[a]	NA	42	-	38
PCB 206[a]	NA	89	-	NC
2,3,7,8-TetraCDD[d]	NA	88	-	NC
1,2,3,7,8-PentaCDD[d]	83	67	NC	NC
1,2,3,4,7,8-HexaCDD[d]	NA	67	-	NC
1,2,3,6,7,8-HexaCDD[d]	52	7	NC	0.25
1,2,3,7,8,9-HexaCDD[d]	82	60	NC	NC
1,2,3,4,6,7,8-HeptaCDD[d]	28	1	0.25	0.28
1,2,3,4,6,7,8,9-OctaCDD[d]	22	19	1.78	2.33
2,3,4,7,8-PentaCDF[d]	47	35	0.03	0.03
1,2,3,4,7,8-HexaCDF[d]	51	18	NC	0.03
1,2,3,6,7,8-HexaCDF[d]	69	31	NC	0.03
2,3,4,6,7,8-HexaCDF[d]	NA	89	-	NC
1,2,3,4,6,7,8-HeptaCDF[d]	45	10	0.04	0.06
Total PCBs[e]	32	3	-	-
Total TEQs[e]	8	0	-	-

CDD=chlorodibenzo-p-dioxin; CDF=chlorodibenzofuran; LOD=limit of detection.

[a]Congener included in sum of PCBs.
[b]NA=not tested or >90% of results below LOD.
[c]NC=not calculated because > 50% of samples below LOD
[d]Congener included in sum of TEQ.
[e]Percent of participants with all congeners in sum PCBs or TEQs below LOD.

Table 2: Serum Total PCBs, Total TEQs, and DDE Levels in 1999-2002 NHANES Participants without Thyroid Disease

Organochlorine	1999-2000 Cycle			2001-2002 Cycle		
	N	Mean[a]	95% CI	N	Mean[a]	95% CI
Sum PCBs (ng/g)	945	0.86*	0.81, 0.92	1406	1.27*	1.20, 1.35
Sum PCBs (ng/g lipid)	945	139.8*	132.1, 147.9	1406	200.3*	189.3, 212.1
Sum TEQs (pg/g)	877	0.08*	0.07, 0.08	1107	0.12*	0.11, 0.13
Sum TEQs (pg/g lipid)	877	12.3*	11.6, 13.0	1107	18.2*	16.6, 19.9
DDE (ng/g)	986	1.82	1.53, 2.17	1443	2.12	1.91, 2.35
DDE (ng/g lipid)	986	293.0	248.0, 346.1	1443	337.0	304.3, 373.1

CI=confidence interval.

[a]Geometric means, all models adjusted for survey design and sample weights.

*Significantly different by study cycle, $p<0.05$.

Table 3: Characteristics of the 1999-2002 NHANES Participants without Thyroid Disease[a]

Characteristic	Men		Women	
	Estimate[b]	95% CI	Estimate[b]	95% CI
N	1166		1279	
Ethnicity, %*				
Caucasian	72.5	67.4, 77.7	68.8	63.9, 73.6
African American	9.4	6.6, 12.1	11.5	7.9, 15.1
Mexican American	8.5	5.9, 11.1	7.3	5.1, 9.5
Other/Mixed	9.6	5.5, 13.6	12.4	8.6, 16.3
Age (years), mean	44.9	43.6, 46.3	45.9	44.6, 47.1
BMI (kg/m^2), geometric mean	27.3	26.9, 27.8	27.0	26.5, 27.5
Total serum lipids (mg/dL), mean	683*	660, 707	652*	639, 665
Cotinine (ng/mL), geometric mean	1.2*	0.8, 1.8	0.4*	0.3, 0.5
Completed menopause, %	NA		45.5	41.9, 49.1
Pregnant, %	NA		3.7	2.6, 4.7
Medication use in the past month:				
Estrogen and/or progesterone, %	NA		21.3	16.9, 25.7
Other steroid hormones, %	2.3	1.1, 3.4	3.2	2.3, 4.1
Furosamide, %	2.2	1.1, 3.4	2.7	1.7, 3.8
Beta-blockers, %	6.7	4.0, 9.5	5.6	4.3, 6.9
NSAID, %	25.9	22.0, 29.8	26.4	22.0, 30.8
Blood glucose regulators, %	5.6	3.9, 7.2	4.4	3.0, 5.9
Other drugs[c], %	0.8	0.3, 1.3	1.0	0.3, 1.7
Thyroid Hormones				
Thyroxine (ug/dL), mean	7.5*	7.3, 7.7	8.2*	8.0, 8.5
Thyroxine, % below 5.4 ug/dL	8.0*	5.3, 10.6	3.2*	1.5, 5.0
Thyroxine, % above 12.8 ug/dL	0.1*	0.0, 0.2	1.5*	0.7, 2.3
TSH (IU/L), geometric mean	1.44	1.39, 1.50	1.46	1.39, 1.53
TSH, % below 0.47 IU/L	2.9	1.5, 4.2	3.8	2.7, 5.0
TSH, % above 5.0 IU/L	2.4	1.4, 3.5	2.3	1.4, 3.2

NA=not applicable. CI=confidence interval. Data was missing for cotinine (n=21), BMI, (n=4), TSH (n=3), pregnancy (n=10) and completion of menopause (n=25).

[a]A total of 36 men and 114 women with thyroid disease (reported current thyroid disease or taking thyroid medications) were excluded from the analysis.

[b]All estimates adjusted for survey design and sample weights.

[c]Other drug category includes use of amidoarone, carbamazepine, chlorpropamide, carbidopa/levodopa, heparin, interferon, lithium, phenytoin, phenobarbital, and sulfasalazine.

*Significantly different by gender, $p<0.05$

Table 4: Associations of Total TEQs and PCBs with Thyroid Hormones in Women without Thyroid Disease

Subgroup	Cycle		Association of Total Thyroxine with:			Association of Ln TSH with:		
			Ln Sum PCBs	Ln Sum TEQs	Ln DDE	Ln Sum PCBs	Ln Sum TEQs	Ln DDE
All Women	1999-2000	Beta[a]	-0.20	-0.19	0.16[b]	-0.03	0.15	-0.01
		95% CI	(-0.47, 0.07)	(-0.70, 0.33)	(-0.04, 0.37)	(-0.30, 0.25)	(-0.14, 0.44)	(-0.12, 0.11)
		N	333	310	350	332	309	350
	2001-2002	Beta[a]	0.09	-0.58[*]	0.11	0.01	0.06	0.08
		95% CI	(-0.42, 0.59)	(-1.26, 0.10)	(-0.07, 0.30)	(-0.17, 0.19)	(-0.15, 0.27)	(-0.03, 0.19)
		N	476	386	490	475	385	489
Women < 60 Years	1999-2000	Beta[a]	-0.08	-0.04	0.33[**,b]	-0.04	0.16	-0.04
		95% CI	(-0.40, 0.25)	(-0.78, 0.69)	(0.04, 0.62)	(-0.36, 0.28)	(-0.14, 0.47)	(-0.16, 0.08)
		N	215	197	219	214	196	219
	2001-2002	Beta[a]	0.20	-0.51	0.08	-0.01	0.04	0.09
		95% CI	(-0.35, 0.76)	(-1.30, 0.29)	(-0.14, 0.29)	(-0.21, 0.19)	(-0.27, 0.35)	(-0.05, 0.22)
		N	327	260	337	326	259	336
Women > 60 Years	1999-2000	Beta[a]	-0.38	-0.40[**]	-0.47[#,b]	0.14	0.00	0.15[*,b]
		95% CI	(-0.89, 0.14)	(-0.71, -0.10)	(-0.74, -0.20)	(-0.17, 0.45)	(-0.48, 0.48)	(-0.01, 0.30)
		N	118	113	131	118	113	131
	2001-2002	Beta[a]	-0.96[#,b]	-1.20[#,b]	0.26[*,b]	0.25[**]	0.23[**]	0.05
		95% CI	(-1.51, -0.41)	(-1.75, -0.64)	(-0.03, 0.55)	(0.05, 0.46)	(0.04, 0.42)	(-0.04, 0.15)
		N	149	126	153	149	126	153

[a]Beta coefficient (95% confidence interval) for effect of organochlorine on thyroid hormone is from linear regression model adjusted for survey design and sample weights, total serum lipids, BMI, race, age, gender, log serum cotinine, menopausal status, and medication use (furosamide, NASIDs, beta-blockers, blood glucose regulators, and other medications). Women who were pregnant, taking steroid hormones and using thyroid medications were excluded.

Effects of organochlorines on thyroid hormones were estimated in models that included concentrations of PCBs, DDE, and TEQs: [b]significant in model including all 3 organochlorines ($p<0.05$).

*$0.05<p<0.1$; **$0.01<p<0.05$; #$p<0.01$

Table 5: Associations of Total TEQs and PCBs with Thyroid Hormones in Men without Thyroid Disease

Subgroup	Cycle		Association of Total Thyroxine with:			Association of Ln TSH with:		
			Ln Sum PCBs	Ln Sum TEQs	Ln DDE	Ln Sum PCBs	Ln Sum TEQs	Ln DDE
All Men	1999-2000	Beta[a]	0.12	-0.12	-0.08	-0.17	-0.09	-0.05
		95% CI	(-0.30, 0.55)	(-0.61, 0.37)	(-0.35, 0.19)	(-0.45, 0.11)	(-0.38, 0.20)	(-0.11, 0.01)
		N	436	402	454	436	402	454
	2001-2002	Beta[a]	-0.31	-0.47*	-0.03	-0.09	-0.02	0.04
		95% CI	(-0.76, 0.15)	(-0.97, 0.04)	(-0.18, 0.24)	(-0.21, 0.04)	(-0.20, 0.16)	(-0.03, 0.10)
		N	653	497	667	653	497	667
Men < 60 Years	1999-2000	Beta[a]	-0.06	-0.27	-0.10	-0.15	-0.05	-0.04
		95% CI	(-0.70, 0.57)	(-0.79, 0.26)	(-0.39, 0.18)	(-0.54, 0.24)	(-0.39, 0.29)	(-0.11, 0.03)
		N	278	252	286	278	252	286
	2001-2002	Beta[a]	-0.41	-0.40	-0.02	-0.09	-0.12	0.02
		95% CI	(-0.92, 0.10)	(-1.05, 0.25)	(-0.26, 0.22)	(-0.24, 0.06)	(-0.38, 0.14)	(-0.05, 0.09)
		N	467	342	472	467	342	472
Men > 60 Years	1999-2000	Beta[a]	0.19	0.25	-0.18[b]	-0.19**	-0.22	-0.09
		95% CI	(-0.36, 0.74)	(-0.36, 0.86)	(-0.47, 0.11)	(-0.38,0.00)	(-0.54, 0.10)	(-0.25, 0.08)
		N	158	150	168	158	150	168
	2001-2002	Beta[a]	0.10	-0.57*,[b]	0.21	-0.18*,[b]	0.19	0.10
		95% CI	(-0.61, 0.81)	(-1.17, 0.32)	(-0.19, 0.60)	(-0.37, 0.01)	(-0.11, 0.49)	(-0.06, 0.26)
		N	186	155	195	186	155	195

[a]Beta coefficient (95% confidence interval) for effect of organochlorine on thyroid hormone is from linear regression model adjusted for survey design and sample weights, total serum lipids, BMI, race, age, gender, log serum cotinine, and medication use (furosamide, NASIDs, beta-blockers, blood glucose regulators, and other medications). Men taking steroid hormones and thyroid medications were excluded.

Effects of organochlorines on thyroid hormones were estimated in models that included concentrations of PCBs, DDE, and TEQs: [b]significant in model including all 3 organochlorines ($p<0.05$).

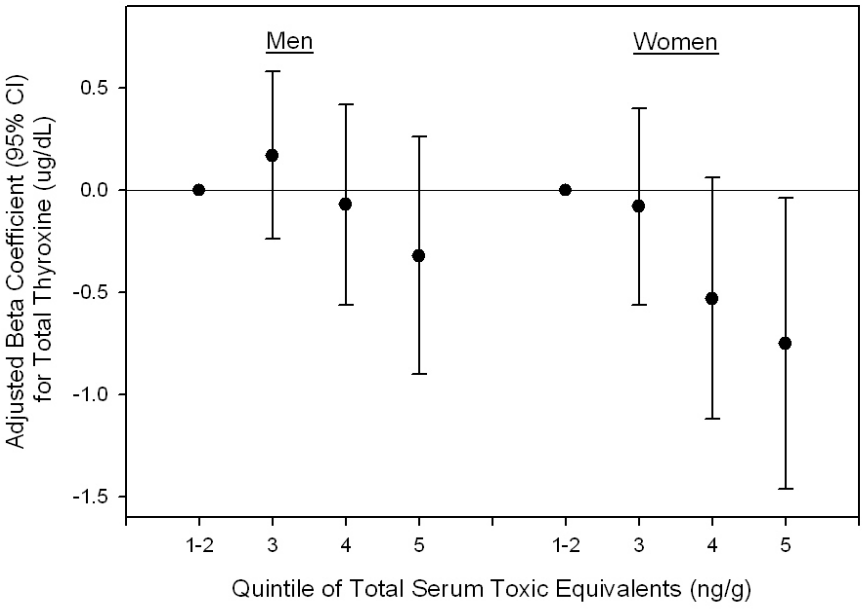
*$0.05<p<0.1$; **$p<0.05$

Figure 1 Legend:

Associations of total thyroxine with total TEQs in participants from both the 1999-2000 and the 2001-2002 NHANES cycles. Total TEQs were ranked into quintiles within each individual cycle, the cycles were merged, and the lowest two quintiles were combined for analysis. Models were adjusted for survey design and sample weights, study cycle, total serum lipids, log BMI, race, age, log serum cotinine, medication use (furosamide, NSAIDs, beta-blockers, blood glucose regulators, and other medications), and menopause status (women only). Participants with thyroid disease, taking thyroid medications, taking steroid hormones, or currently pregnant were eliminated from analyses.

Adjusted beta coefficients and 95% confidence intervals for trends across quintiles were -0.09 (-0.28, 0.10) for men ($p=0.28$, $n=899$); and -0.25 (-0.48, -0.02) for women ($p=0.03$, $n=696$). With further control for DDE, trend across quintiles remained significant for women ($p<0.05$). With further control for total PCBs, results were of borderline significance for women ($p=0.07$).

Figure 1


Men
Women
0.5
0.0
-0.5
-1.0
-1.5
Adjusted Beta Coefficient (95% CI)
for Total Thyroxine (ug/dL)
1-2
3
4
5
1-2
3
4
5
Quintile of Total Serum Toxic Equivalents (ng/g)