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Relationship between Urinary Triclosan and Paraben Concentrations and Serum Thyroid Measures in NHANES 2007–2008

Erika S. Koeppe[1], **Kelly K. Ferguson**[1], **Justin A. Colacino**[1], and **John D. Meeker**[1]
[1]Department of Environmental Health Sciences, University of Michigan School of Public Health Ann Arbor, MI

Abstract

Triclosan and parabens are broad spectrum antimicrobials used in a range of consumer products. *In vitro* and animal studies have suggested the potential for these compounds to disrupt thyroid function, though studies in humans have been limited. The objective of the study was to assess the relationship of urinary concentrations of triclosan and parabens with serum thyroid measures in a large, representative sample of the US population. We conducted an exploratory, cross-sectional analysis of data on urinary biomarkers of triclosan and paraben exposure and serum thyroid measures obtained from 1,831 subjects (ages ≥12 years) as part of the 2007–2008 National Health and Nutrition Examination Survey (NHANES). We found evidence of some inverse associations between parabens and circulating thyroid hormone levels in adults, with the strongest and most consistent associations among females. We also observed a positive association between triclosan and total triiodothyonine (T3) concentrations in adolescents. These results, in accordance with the *in vitro* and animal literature, suggest that paraben, and potentially triclosan, exposures may be associated with altered thyroid hormone levels in humans. Further research is needed for confirmation and to determine the potential clinical significance of these findings.

Keywords

Biomarkers; endocrine disruptors; phenols

1. Introduction

The broad-spectrum antimicrobials triclosan and parabens are widely used in consumer products, but have poorly characterized health effects. Triclosan (2, 4, 4′-trichloro-2′-hydroxydiphenyl ether) was originally synthesized in 1972 and has since been incorporated as an antibacterial agent in toothpaste, mouthwash, soaps, deodorants, textiles, toys, medical devices, and kitchenware (Dann and Hontela, 2011). Parabens, the esters of *para*-hydroxybenzoic acid, were first used as preservatives by the pharmaceutical industry in the

Corresponding Author: John D. Meeker, ScD, University of Michigan School of Public Health, Department of Environmental Health Sciences, M6017 SPH II, 109 S. Observatory St. Ann Arbor, MI 48109, Phone: 1-734-764-7184, Fax: 1-734-936-7283, meekerj@umich.edu.

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1920s. In the last several decades, their applications have expanded to cosmetics, lotions, skin cleansers, hair and shaving products, and, to a lesser extent, as anti-spoiling agents in foods and food packing materials (Soni et al., 2005).

Recent evidence suggests that triclosan and parabens may have previously unrecognized endocrine disrupting properties (EPA, 2010). Research to this end has predominantly suggested impacts to the reproductive axis (Darbre and Harvey, 2008; Foran et al., 2000; Ishibishi et al., 2004; Raut and Angus, 2010); however, there has been growing interest in the thyroid axis as a susceptible target (Zoeller, 2007). Thyroid hormones (THs), which consist of triiodothyonine (T3) and thyroxine (T4), play a critical role in fetal and child growth and neurodevelopment, are essential in regulating metabolism and maintaining energy balance, and carry out a range of functions in the nervous, cardiovascular, skeletal, pulmonary, and reproductive systems (Dussault and Ruel, 1987; Stathatos, 2012). Exogenous chemicals that disrupt TH homeostasis, particularly during key developmental periods, can cause a number of adverse health outcomes, including profound effects on the normal development of the brain (Porterfield and Hendrich, 1993).

The propensity of triclosan and similar phenols such as parabens to disrupt thyroid function has been hypothesized based on the structural similarity of these compounds to THs (Allymyr et al., 2009; Crofton et al., 2007; Dann and Hontela, 2011). While a number of *in vitro* studies have suggested mechanisms by which these chemicals may exert thyroid disrupting effects (Jinno et al., 1997; Rousset, 1981; Schuur et al., 1998; Taxvig et al., 2008; Wang et al., 2004), direct impacts of triclosan and paraben exposures on TH levels have only recently been investigated in rat models. These studies have demonstrated the ability of triclosan and parabens to decrease TH levels *in vivo* (Crofton et al., 2007; Paul et al., 2010; Vo et al., 2010; Zorrilla et al., 2009). Publications of human data examining thyroid endpoints in relation to triclosan and paraben exposure have been scarce, and have not identified any significant associations, although sample sizes were small (Allmyr et al., 2009; Cullinan et al., 2012; Janjua et al., 2007; Meeker et al., 2011). Overall, thyroid outcomes relative to triclosan and paraben exposure remain largely uncharacterized in humans. This assessment aims to describe the association between triclosan and paraben exposure and thyroid function in a large, nationally representative, human population.

2. Methods

Data was obtained from the 2007–2008 National Health and Nutrition Examination Survey (NHANES) cycle. NHANES is an ongoing, cross-sectional study conducted by the Centers for Disease Control and Prevention (CDC) to evaluate the health and dietary status of the US population. Methods of survey data collection are described in detail elsewhere (NCHS 2010a). Briefly, a stratified multistage probability sample of the civilian non-institutionalized population of the US is surveyed via household interviews, physical examinations, and collection of medical histories and biologic specimens.

2.1. Urinary biomarkers

Urinary biomarkers for triclosan, methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), butyl paraben (BP) were measured in a nationally representative, one-third subset of the NHANES population aged 6 years and older. Spot urine samples were collected at Mobile Examination Centers and shipped on dry ice to the CDC's National Center for Environmental Health, where they were stored at −20°C until analysis. Following hydrolysis of conjugated species by use of β-glucuronidase/sulfatase, individual parabens and triclosan were measured using online solid phase extraction (SPE), reversed-phase high-performance liquid chromatography separation, and atmospheric pressure chemical ionization-isotope dilution and tandem mass spectrometry (MS/MS), as described in detail elsewhere (Ye et al.,

2005; Ye et al., 2006). Quality assurance and quality control (QA/QC) procedures were carried out for all analytes according to specifications described by Westgard et al. (1981). Limit of detection (LOD) values were estimated as $3S_o$, where S_o is the standard deviation as biomarker concentrations approached zero (Taylor, 1987 as referred in Calafat et al., 2008). LODs were 1.0 μg/L for MP and EP; 0.2 μg/L for PP and BP; and 2.3 μg/L for triclosan.

2.2. Serum thyroid measures

Thyroid outcomes were evaluated by the NHANES Thyroid Profile, which includes measurements of free and total T3 and T4, thyroglobulin, and thyroid stimulating hormone (TSH or thyrotropin). Serum samples were collected from participants 12 years and older and measured using immunoenzymatic assays as described in detail elsewhere (NCHS, 2009). QA/QC was performed in accordance with the 1988 Clinical Laboratory Improvement Act mandates. With the exception of total T3 and total T4, all thyroid measurement distributions were right-skewed and ln-transformed prior to analysis.

2.3. Covariates

Covariates selected for consideration as potential confounders included age, sex, body mass index (BMI), urinary iodine, urinary creatinine, race/ethnicity, poverty income ratio (PIR, an indicator of socioeconomic status), education, serum cotinine (a surrogate for exposure to tobacco smoke) and alcohol intake. Variables used as the basis for creation of sample weights, including race/ethnicity, PIR, and education, were not included in final models to avoid over-adjustment (Korn and Grubard, 1991). Also, urinary iodine was excluded because it has been suggested that iodine may be a mechanistic intermediate in the process of thyroid disruption by MP (Rousset, 1981). Following the ln-transformation of the remaining variables with log-normal distributions, Pearson correlations, one-way analysis of variance procedures (ANOVA), and t-tests were used to evaluate potential confounders' association with urinary exposure biomarkers and serum thyroid measures. A forward stepwise procedure was then employed to evaluate the influence of these covariates in multivariate linear regression models. Covariates were adjusted for in the final models if they were significantly associated with one exposure or outcome variable based on a priori evidence or in our analysis, and if they altered parameter estimates of the main effects by more than 10 percent. Final regression models included age, sex, BMI, and urinary creatinine. For consistency, all models were adjusted for the same covariates.

2.4. Statistical analysis

Of the 2,036 individuals in the 2007–2008 NHANES dataset with at least one urinary exposure biomarker and one serum thyroid measurement, we excluded 164 subjects with a history of thyroid disease, 20 who were pregnant, and three with influential outlying values. An additional 18 subjects were excluded from the multivariate regression analysis due to missing BMI measures, resulting in a final sample size of 1,831.

In descriptive analyses as well as in regression models we stratified by age to compare results in adolescents (ages 12–19) and adults (ages 20+) because thyroid activity is thought to differ by these subgroups (Westgren et al., 1976). We calculated geometric means for biomarkers with >30% above the LOD and arithmetic means for biomarkers with normal distributions (total T3 and total T4), as well as medians, ranges, and distribution percentiles for each urinary exposure biomarker and serum thyroid measure. Concentrations of urinary exposure biomarkers below the LOD were replaced in the NHANES dataset with values equal to the LOD divided by the square root of two. Distributions of triclosan and all four paraben biomarkers were right-skewed, thus ln-transformations were performed prior to analysis. Additionally, all thyroid measurement distributions were right-skewed and ln-

transformed prior to analysis, with the exception of total T3 and total T4. Triclosan and parabens were analyzed on a creatinine-adjusted basis for univariate and bivariate analyses. Unadjusted urinary exposure biomarker concentrations were used in regression models with urinary creatinine included as a covariate (Barr et al., 2005).

Final multivariate linear regression models included serum thyroid concentrations (continuous variable) as the dependent variable and an individual urinary triclosan, MP, and PP concentration (continuous) as a predictor, along with age (continuous), sex (dichotomous), BMI (continuous), and ln-transformed urinary creatinine (continuous). To examine possible effect modification, models were additionally stratified on gender. We also explored non-linear relationships by modeling thyroid measures in relation to quartiles of urinary MP, PP or triclosan. Since EP and BP concentrations fell below the LOD for >50% of subjects, we evaluated their associations with thyroid hormone levels using dichotomous predictors representing exposure biomarker concentrations at or above the LOD versus those below the LOD. These models were adjusted for the same covariates and similarly stratified.

Data analysis was performed using SAS software (version 9.2; SAS Institute, Cary, NC). SAS survey procedures with the appropriate strata, cluster, and weights were applied as described in the NCHS web tutorial (NCHS 2010b) to account for the complex, multistage study design of NHANES.

3. Results

Distributions of creatinine-adjusted triclosan and paraben concentrations among adults and adolescents stratified by gender are described in Table 1. Serum thyroid measure distributions among adults and adolescents are shown in Table 2. In bivariate analysis, urinary biomarker concentrations of all four parabens and triclosan were significantly elevated in females compared with males ($P<0.05$). Age was positively associated with triclosan, EP, and BP concentrations ($P<0.05$), while BMI was inversely associated with paraben concentrations ($P<0.05$). All of the aforementioned covariates demonstrated associations with at least one serum thyroid measure at the alpha=0.05 level. Within the exposure variables, MP and PP levels were strongly correlated (R = 0.8*2, P* <0.0001). EP and BP exhibited moderate correlations with each other (R= 0.57, $P<0.0001$) and with MP and PP (R values ranging from 0.48 to 0.50, $P<0.0001$), although these results may be due in part to the substantial percentage of samples below the LOD for these analytes. Triclosan was weakly but significantly correlated with each paraben (R<0.2, $P<0.0001$).

Results of the multivariate regression stratified by age group are presented in Table 3. In adults (ages≥20; N=1,479), PP exhibited a significant inverse association with total T4 (β= −0.05, $P=0.04$) and a suggestive inverse association with free T4 (β=−0.004, $P=0.06$). In regression analyses using dichotomous predictors to represent EP and BP concentrations at or above versus below the LOD, detection of EP was associated with a significant decrease in total T4 (β=−0.20, $P=0.03$). The sample size for the adolescent models (ages 12–19; N=352) was considerably smaller than that for adults, and statistically significant associations between parabens and TH levels were not observed among this segment of the population; however an inverse association between MP and free T3 approached significance (β=−0.01, $P=0.07$). Additionally, a unique positive association between triclosan and total T3 emerged (β=1.96, $P=0.04$), where an interquartile range (IQR) increase in urinary triclosan concentration was associated with a 3.8% increase in total T3 levels (95th CI 0.1%, 7.5%) relative to the median total T3 concentration in adolescents.

In subsequent analyses, both adult and adolescent multivariate regression models were stratified by gender (Table 4 and 5, respectively). In adults, there were no significant associations between exposure biomarkers and TH levels among males, with the exception

of a positive association between EP detection and free T4 which approached significance ((β=0.02, *P*=0.06). In adult females, increased urinary PP concentrations were associated with significant decreases in free T3 (β=−0.006, *P*=0.02) and free T4 (β=−0.01, *P*=0.01), and there were suggestive inverse associations between urinary MP with free T3 (β=−0.005, *P*=0.057) and free T4 (β=−0.01, *P*=0.055). Based on these results, an IQR increase in PP was associated with a 1.6% decrease in free T3 (95th CI 0.3%, 2.6%) and a 2.6% decrease in free T4 (95th CI 0.8%, 5.1%). Inverse relationships were also observed for dichotomous EP and BP exposure variables and serum thyroid measures among adult females. Detectable levels of EP were associated with diminished free T3 (*P*=0.03), free T4 (*P*=0.03), and total T4 levels (*P*=0.002), while detectable BP was associated with lower levels of free T3 (*P*=0.03). For example, for an adult female with median concentrations of THs, detection of EP was associated with a 4.2% decline in total T4 (95th CI 1.9%, 6.7%), 3.9% decline in free T4 (95th CI 0.4%, 6.8%), and 2.0% decline in free T3 (95th CI 0.2%, 3.0%). Detection of BP was associated with a 2.0 % decrease in free T3 levels (95th CI 0.2%, 3.9%).

Statistically significant associations were not demonstrated among adolescents following gender-stratification, although adolescent females exhibited suggestive inverse associations between MP and free T3 (β=−0.02, *P*=0.13) as well as PP and free T3 (β=−0.01, *P*=0.10). No statistically significant associations were observed between exposure biomarkers and serum thyroglobulin or TSH measures in any of our analyses, including those with adults, adolescents, or either age group stratified by sex (See Supplemental Material). Finally, an analysis of urinary PP, MP or triclosan quartiles in relation to thyroid measures supported findings from our primary analyses, where inverse trends were observed between parabens and TH, especially among women (See Supplemental Material).

4. Discussion

In this analysis of data from 2007–2008 NHANES, we found evidence of inverse associations of all parabens with TH levels in female adults, but not in males. Detection of urinary EP or BP concentrations was similarly associated with decreases in THs. Triclosan did not exhibit significant associations with TH levels, with the exception of a positive relationship between triclosan and total T3 concentrations in adolescents.

We identified consistently negative associations between parabens and THs, which has been suggested by previous *in vitro* and animal studies. An *in vitro* study conducted in hog thyroid cells found that MP prevented the synthesis of THs by thwarting iodide organification, a key step in TH formation (Rousset, 1981). In a study of rats dosed with 200–400 mg/kg/day of EP and BP, an *in vitro* assay indicated that BP acted as a weak TH receptor (TR) agonist (Taxvig et al., 2008). Most recently, an *in vivo* study reported that rats underwent significant thyroid gland weight gain when exposed to MP and BP doses of 1000 mg/kg BW/day (Vo et al., 2010). Such a weight change might be explained by activation of a feedback loop in response to low TH blood levels, stimulating the thyroid gland to produce more THs and potentially leading to hypertrophy and corresponding increase in thyroid gland weight (Zabka et al., 2011). The same study by Vo et al. (2010) also demonstrated that exposure to doses ranging from 62.5 to 1000 mg/kg BW/day of MP, PP, isopropyl paraben, and isobutyl paraben significantly diminished T4 levels. In summary, *in vitro* and animal studies to date have suggested inverse associations between parabens and THs at high doses. The direction of these associations is congruent with our findings in this observational study among humans with much lower and environmentally relevant levels of exposure. Our observation of effects at environmentally relevant doses, and the fact that the mere detection of EP and BP was associated with TH changes, may be supported by emerging patterns in this area, which suggest that endocrine-disrupting chemicals commonly exhibit low-dose and non-monotonic effects (Vandenberg et al., 2012).

In a previous human study of parabens and thyroid function, TH levels remained unchanged following topical application of a cream containing BP and diethyl and dibutyl phthalate (Janjua et al., 2007). This study involved a relatively small sample size (n=26), which may have been underpowered to detect TH alterations in relation to these compounds. In a study of 167 men recruited though an infertility clinic, no associations were identified between urinary parabens and thyroid measures (free T4, total T3, or TSH) (Meeker et al., 2011). To the best of our knowledge, there are no other studies of parabens in humans with which to compare these findings.

The present study's finding of associations between parabens and THs among females but not males might be explained by gender-related differences in use patterns of personal care products, which represent a dominant source of exposure. As was evidenced by the data, paraben concentrations are significantly elevated in women compared to men, with a high degree of between-individual variability, potentially allowing for a greater opportunity to observe relationships between parabens and thyroid function. Evidence for stronger associations among women deserves further attention, particularly since women of child-bearing age comprise a uniquely sensitive segment of the population, and thyroid disruption during pregnancy can result in severe and irreversible impacts to the developing fetus (Stathatos, 2012).

The results among adolescents (ages 12–19) generally did not conform to those among adults. The geometric mean, median, and quintile urinary concentrations of triclosan and parabens were consistently lower in this younger age group. It is therefore possible that it was more difficult to detect associations in TH levels due to lower excreted levels in this group. The sample size was also substantially smaller for this age group (352 compared with 1,479 adults), which decreased the statistical power. Nevertheless, we did find evidence of suggestive inverse associations between parabens and thyroid measures in adolescent females similar to those seen in adult females. Lastly, we observed a significant positive association between triclosan and total T3 levels among this age group, which deserves further attention in larger studies of adolescent populations.

To our knowledge, this is the first human study to investigate triclosan exposure and thyroid function in an adolescent population. Two previous human studies examined exposure to triclosan-containing toothpaste in 12 healthy adult volunteers (Allmyr et al., 2009) and 132 cardiovascular patients with an average age of 62 (Cullinan et al., 2012). Neither of these studies detected changes in serum TH in exposed individuals, potentially as a result of small sample sizes. Rat studies have consistently identified inverse associations between triclosan and serum T3 (Crofton et al., 2007; Paul et al., 2010; Rodriguez and Sanchez, 2010; Zorilla et al., 2009). It is uncertain whether the mechanisms by which thyroid disruption occurs in rats are the same as those in humans, and it is possible that triclosan could have multiple modes of action. *In vitro* studies have suggested that triclosan may inhibit sulfotransferase (SULT) and uridine diphospho-glucuronosyl-transferases enzyme activity associated with Phase II thyroid metabolism (Schurr et al, 1998; Wang et al, 2004). The rate-limiting step in biliary excretion is sulfation for T3 and glucuronidation for T4 (Klaassen and Watkins, 2010). Our observation of a significant increase in T3, but not T4 concentrations among adolescents, may support SULT inhibition as the major mechanism of action in this subset of the population. Given that triclosan was only positively associated with total T3 among adolescents while adults had higher excreted triclosan levels, it is possible this association was observed due to differences in distribution kinetics, metabolism, or other susceptibility factors between adolescent and adults. It is also possible that this finding was the result of residual confounding or chance.

There were no significant changes in serum TSH and thyroglobulin concentrations in association with triclosan or paraben exposures revealed during our analysis. Based on the negative feedback relationship between serum TH and TSH levels, we might expect to see a positive association between TSH and parabens accompanying reduced TH concentrations. However, a number of other chemicals have been reported to cause a decrease in TH levels without increasing serum TSH, most notably PCBs (Martin and Klaassen, 2010; Zoeller, 2010). The mechanisms by which xenobiotics can diminish serum THs without altering TSH levels are poorly understood (Zoeller, 2010).

The present assessment has several limitations. NHANES is an observational, cross-sectional study, thus causality cannot be established. Furthermore, exposures were evaluated on the basis of spot urine measurements. The relatively short half-lives of triclosan and parabens in the body (under 24 hours), indicates that time of sample collection could be a source of intra-individual variability and that spot urine concentrations may not accurately represent a subject's average body burden. However, a recent study evaluating 2,721 spot urine samples calculated intraclass correlation coefficients for MP and PP of 0.42 and 0.43 respectively in women, and 0.54 and 0.51 in men, and concluded that a single urine sample may reliably represent paraben exposure over several months (Smith et al., 2012). Previous analyses of NHANES did not find time of urine collection to be a significant factor in explaining the variance of triclosan or parabens (Calafat et al., 2008; 2010).

In conclusion, the present analysis was the first to examine the relationship between triclosan, parabens, and serum TH levels in a large, representative sample of U.S. adults and adolescents. NHANES data from 1,831 individuals afforded us sufficient statistical power to detect small-scale associations and dramatically increased the generalizability of findings compared to previous human studies. We observed significant inverse associations between paraben and TH concentrations in women, as well as a positive association between triclosan and T3 in adolescents. Additional human studies with repeated urine and blood samples to estimate exposure and TH concentrations are needed for confirmation and to determine the potential clinical significance of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	Body mass index
BP	Butyl paraben
CDC	US Centers for Disease Control and Prevention
EP	Ethyl paraben
IQR	Interquartile range
LOD	Limit of detection

MP	Methyl paraben
NHANES	National Health and Nutrition Examination Survey
PP	Propyl paraben
QA/QC	Quality assurance/Quality control
SULT	Sulfotransferase
T3	Triiodothyonine
T4	Thyroxine
TG	Thyroglobulin
TCS	Triclosan
TH	Thyroid hormone
TR	Thyroid hormone receptor
TSH	Thyroid stimulating hormone; thyrotropin
US	United States

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Highlights

- Triclosan and parabens are widely used in the US and elsewhere.
- Biomarkers of exposure were examined in relation to serum thyroid hormone levels.
- In adults, we observed inverse associations between parabens and thyroid hormones.
- In adolescents, we observed positive associations between triclosan and total T3.
- Future research is necessary to confirm findings and explore clinical relevance.

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Table 1

Exposure biomarker distributions stratified by age group and gender[a]

Creatinine-adjusted urinary triclosan and paraben concentrations (μg/g creatinine)								
	% <LOD	**Geomean**	**25th Perc.**	**Median**	**75th Perc.**	**90th Perc.**	**95th Perc.**	**Max.**
Adolescent males, ages 12–19. N=185								
Triclosan	18.9	12.7	3.40	10.4	46.7	141	258	586
Butyl paraben	66.0	NC	0.09	0.14	0.30	0.84	2.30	123
Ethyl paraben	70.8	NC	0.43	0.66	1.68	3.38	8.36	629
Methyl paraben	1.08	26.3	8.59	20.8	86.0	191	310	2924
Propyl paraben	4.86	2.38	0.59	1.75	5.65	30.6	70.0	480
Adolescent females, ages 12–19. N=171								
Triclosan	14.0	15.0	4.09	11.5	39.4	258	501	1112
Butyl paraben	36.8	NC	0.15	0.30	1.46	7.84	18.2	116
Ethyl paraben	40.4	NC	0.72	1.55	5.71	34.5	81.2	626
Methyl paraben	0.0	93.7	36.6	97.5	267	418	609	5571
Propyl paraben	0.0	20.9	6.29	26.1	86.2	119	230	1002
Adult males, ages ≥ 20. N=785								
Triclosan	21.5	13.5	3.02	10.6	51.1	224	361	2388
Butyl paraben	73.1	NC	0.09	0.13	0.26	0.83	2.27	723
Ethyl paraben	59.9	NC	0.54	0.86	1.97	8.17	18.8	771
Methyl paraben	0.38	26.9	8.63	21.9	76.6	240	438	7909
Propyl paraben	9.94	2.47	0.50	1.65	11.4	44.7	122	1486
Adult females, ages ≥20. N=708								
Triclosan	19.2	19.9	5.27	15.6	57.5	320	621	2468
Butyl paraben	34.6	NC	0.28	1.06	7.62	25.3	46.9	309
Ethyl paraben	39.7	NC	1.13	3.52	18.5	70.1	130	3010
Methyl paraben	0.14	151.4	61.6	196	421	760	1061	4282
Propyl paraben	2.54	26.8	7.98	39.1	110	217	341	990

Geomean, geometric mean.

NC, value was not calculated due to high percentage of measurements below the LOD.

[a] Results weighted for sample design.

Table 2

Serum thyroid hormone distributions stratified by age group[a]

Serum thyroid hormone concentration							
	Geomean	**25th Perc.**	**Median**	**75th Perc.**	**90th Perc.**	**95th Perc.**	**Max.**
Adolescents, ages 12–19. N=356							
Free T3 (pg/mL)	3.58	3.26	3.53	3.79	4.02	4.29	5.70
Total T3 (ng/dL)	131[b]	114	127	144	164	174	212
Free T4 (ng/dL)	0.78	0.65	0.74	0.81	0.89	0.95	1.20
Total T4 (ug/dL)	7.55[b]	6.48	7.23	8.26	9.27	10.3	18.5
Thyroglobulin (ng/mL)	7.79	5.44	9.17	14.5	19.0	22.8	69.3
Thyrotropin (uIU/mL)	1.44	1.03	1.48	2.09	2.77	3.15	6.31
Adults, ages ≥20. N=1493							
Free T3 (pg/mL)	3.17	2.89	3.12	3.35	3.57	3.73	5.20
Total T3 (ng/dL)	112[b]	96.7	110	124	140	150	218
Free T4 (ng/dL)	0.76	0.63	0.71	0.79	0.88	0.93	1.70
Total T4 (ug/dL)	7.59[b]	6.56	7.41	8.35	9.46	10.2	17.9
Thyroglobulin (ng/mL)	9.94	6.23	10.1	17.7	29.2	41.6	4491
Thyrotropin (uIU/mL)	1.61	1.09	1.63	2.36	3.36	4.47	39.0

Geomean, geometric mean.

[a]Results weighted for sample design.

[b]Arithmetic mean.

Table 3

Adjusted[a] regression coefficients (95th CI) for change in serum thyroid measure in relation to a unit increase in ln-transformed urinary triclosan or paraben concentration stratified by age group.

	Ln-Free T3 (pg/mL)		Total T3 (ng/dL)		Ln-Free T4 (ng/dL)		Total T4 (μg/dL)	
	β (95th CI)	p-value	β (95th CI)	p-value	β (95th CI)	p-value	β (95th CI)	p-value
Adolescents, ages 12–19. N=352[c]								
TCS	0.002 (−0.01, 0.01)	0.72	1.96 (0.05, 3.88)	0.04	−0.002 (−0.02, 0.01)	0.80	0.008 (−0.11, 0.12)	0.89
MP	−0.01(−0.02, 0.001)	0.07	−0.58 (−2.89, 1.74)	0.61	0.005 (−0.01, 0.02)	0.50	0.004 (−0.13, 0.13)	0.94
PP	−0.004 (−0.01, 0.01)	0.43	0.18 (−1.93, 2.29)	0.86	0.006 (−0.01, 0.02)	0.40	−0.008 (−0.13, 0.12)	0.89
BP[b]	0.006 (−0.02, 0.04)	0.70	7.22 (−1.91, 16.3)	0.11	−0.005 (−0.04, 0.03)	0.77	0.12 (−0.32, 0.56)	0.58
EP[b]	−0.006 (−0.04, 0.03)	0.77	3.51(−2.56, 9.58)	0.24	−0.02 (−0.06, 0.02)	0.36	0.02 (−0.34, 0.39)	0.89
Adults, ages =20. N=1479[c]								
TCS	−0.001 (−0.003, 0.001)	0.15	−0.006 (−0.88, 0.86)	0.99	0.000 (−0.01, 0.01)	0.93	−0.005 (−0.07, 0.06)	0.86
MP	−0.002 (−0.01, 0.002)	0.33	0.22 (−0.83, 1.27)	0.66	−0.002 (−0.01, 0.002)	0.32	−0.04 (−0.12, 0.03)	0.26
PP	−0.002 (−0.004, 0.001)	0.17	−0.16 (−0.90, 0.57)	0.65	−0.004 (−0.01, 0.000)	0.06	−0.05 (−0.10, −0.002)	0.04
BP[b]	−0.01(−0.02, 0.005)	0.17	−1.28 (−3.59, 1.03)	0.26	0.0004 (−0.03, 0.03)	0.97	−0.19 (−0.46, 0.07)	0.15
EP[b]	−0.01 (−0.02, 0.004)	0.15	−2.68 (−5.67, 0.39)	0.08	−0.01 (−0.03, 0.01)	0.49	−0.20 (−0.36, −0.03)	0.03

CI, confidence interval.

[a]Adjusted for age, sex, BMI, ln-urinary creatinine; results weighted for sample design.

[b]Predictors coded as dichotomous variables; regression coefficient represents change in serum thyroid measure in relation to having a detectable urinary exposure biomarker concentration.

[c]BMI data missing on 4 adolescents and 14 adults.

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Table 4

Adjusted[a] regression coefficients (95th CI) for change in serum thyroid measure in relation to a unit increase in ln-transformed urinary triclosan or paraben concentration among adults (ages≥20) stratified by gender.

	Ln-Free T3 (pg/mL)		Total T3 (ng/dL)		Ln-Free T4 (ng/dL)		Total T4 (μg/dL)	
	β (95th CI)	p-value	β (95th CI)	p-value	β (95th CI)	p-value	β (95th CI)	p-value
Adult males, ages ≥20. N=777[c]								
TCS	−0.002 (−0.01, 0.002)	0.33	0.11 (−1.08, 1.30)	0.85	0.007 (−0.003, 0.02)	0.17	−0.005 (−0.08, 0.07)	0.89
MP	0.001 (−0.004, 0.01)	0.75	0.06 (−1.17, 1.29)	0.92	0.005 (−0.002, 0.01)	0.17	−0.006 (−0.09, 0.81)	0.89
PP	0.001 (−0.002, 0.004)	0.41	−0.11 (−0.88, 0.67)	0.77	0.003 (−0.003, 0.01)	0.29	−0.03 (−0.08, 0.03)	0.37
BP[b]	0.004 (−0.02, 0.03)	0.69	0.85 (−2.43, 4.14)	0.59	0.02 (−0.01, 0.06)	0.21	−0.09 (−0.44, 0.27)	0.61
EP[b]	−0.002 (−0.02, 0.02)	0.84	−2.00 (−6.82, 2.82)	0.39	0.02 (−0.001, 0.05)	0.06	−0.05 (−0.34, 0.24)	0.72
Adult females, ages ≥20. N=702[c]								
TCS	0.000 (−0.01, 0.004)	0.81	−0.10 (−1.57, 1.37)	0.89	−0.007 (−0.02, 0.002)	0.12	−0.008 (−0.11, 0.09)	0.86
MP	−0.005 (−0.01, 0.000)	0.057	0.42 (−0.85, 1.69)	0.50	−0.01 (−0.03, 0.000)	0.055	−0.09 (−0.26, 0.08)	0.29
PP	−0.006 (−0.01, −0.001)	0.02	−0.25 (−1.31, 0.82)	0.63	−0.01 (−0.02, −0.003)	0.01	−0.08 (−0.20, 0.05)	0.20
BP[b]	−0.02 (−0.04, −0.002)	0.03	−3.33 (−7.21, 0.56)	0.09	−0.02 (−0.05, 0.01)	0.15	−0.30 (−0.65, 0.06)	0.09
EP[b]	−0.02 (−0.03, −0.002)	0.03	−3.22 (−8.40, 1.96)	0.21	−0.04 (−0.07, −0.004)	0.03	−0.36(−0.57, −0.16)	0.002

CI, confidence interval.

[a]Adjusted for age, BMI, ln-urinary creatinine; results weighted for sample design.

[b]Predictors coded as dichotomous variables; regression coefficient represents change in serum thyroid measure in relation to having a detectable urinary exposure biomarker concentration.

[c]BMI data missing on 8 adult males and 6 adult females.

Table 5

Adjusted[a] regression coefficients (95th CI) for change in serum thyroid measure in relation to a unit increase in ln-transformed urinary triclosan or paraben concentration among adolescents (ages 12–19) stratified by gender.

	Ln-Free T3 (pg/mL)		Total T3 (ng/dL)		Ln-Free T4 (ng/dL)		Total T4 (μg/dL)	
	β (95th CI)	p-value	β (95th CI)	p-value	β (95th CI)	p-value	β (95th CI)	p-value
Adolescent males, ages 12–19. N=184[c]								
TCS	0.004 (−0.01, 0.02)	0.50	1.82 (−0.51, 4.15)	0.12	−0.007 (−0.02, 0.004)	0.19	−0.03 (−0.15, 0.09)	0.56
MP	−0.007 (−0.02, 0.002)	0.12	−0.83 (−3.18, 1.53)	0.47	0.008 (−0.01, 0.03)	0.41	−0.05 (−0.22, 0.11)	0.51
PP	0.002 (−0.01, 0.01)	0.71	−0.16 (−1.79, 1.47)	0.84	0.01 (−0.01, 0.03)	0.28	−0.05 (−0.15, 0.06)	0.38
BP[b]	0.03 (−0.01, 0.08)	0.15	8.47 (−1.14, 18.1)	0.08	0.006 (−0.04, 0.05)	0.79	0.009 (−0.38, 0.40)	0.96
EP[b]	0.01 (−0.04, 0.07)	0.65	0.63 (−10.8, 12.1)	0.91	−0.02 (−0.05, 0.02)	0.41	−0.34 (−0.69, 0.005)	0.053
Adolescent females, ages 12–19. N=168[c]								
TCS	−0.001 (−0.01, 0.009)	0.79	1.90 (−1.07, 4.87)	0.19	0.004 (−0.02, 0.03)	0.64	0.03 (−0.17, 0.23)	0.73
MP	−0.02 (−0.04, 0.01)	0.13	−0.42 (−4.43, 3.60)	0.83	0.001 (−0.02, 0.03)	0.91	0.07 (−0.16, 0.30)	0.53
PP	−0.01 (−0.03, 0.003)	0.10	0.35 (−3.05, 3.75)	0.83	0.001 (−0.02, 0.03)	0.92	0.04 (−0.22, 0.29)	0.78
BP[b]	−0.03 (−0.09, 0.03)	0.33	2.85 (−9.18, 14.9)	0.62	−0.01 (−0.06, 0.03)	0.54	0.07 (−0.83, 0.97)	0.87
EP[b]	−0.03 (−0.09, 0.03)	0.29	5.63 (−5.19, 16.4)	0.29	−0.02 (−0.10, 0.06)	0.57	0.33 (−0.30, 0.95)	0.28

CI, confidence interval.

[a]Adjusted for age, BMI, ln-urinary creatinine; results weighted for sample design.

[b]Predictors coded as dichotomous variables; regression coefficient represents change in serum thyroid measure in relation to having a detectable urinary exposure biomarker concentration.

[c]BMI data missing on 1 adolescent male and 4 adolescent females.