

Research Article



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Abbreviations

BMI: body mass index; CLIA:
chemiluminescence immunoassay; GM:
geometric mean; CI: confidence interval;
KoNEHS: Korean National Environmental
Health Survey; LOD: limit of detection; T3:
triiodothyronine; T4: thyroxine; TSH: thyroid-
stimulating hormone; Triclosan: 5-chloro-2-
(2,4-dichlorophenoxy)phenol.

Relationship between triclosan exposure and thyroid hormones: the Second Korean National Environmental Health Survey (2012–2014)

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ABSTRACT

Background: 5-chloro-2-(2,4-dichlorophenoxy)phenol (triclosan) is used as an antiseptic and is a potential endocrine-disrupting chemical that can affect thyroid hormone levels. This study evaluated the relationship between triclosan exposure and thyroid hormones.

Methods: Data from the second Korean National Environmental Health Survey (2012–2014) were analyzed. Triclosan exposure was evaluated using urinary triclosan concentrations and classified into 2 groups: ‘below detection (< limit of detection [LOD])’ vs. ‘detected (\geq LOD).’ Multiple linear regression analysis was conducted to determine the relationship between triclosan exposure and the serum thyroid hormone concentrations, adjusting for age, body mass index, urinary creatinine, and smoking status.

Results: When grouped by sex, triclosan exposure was positively associated with the serum thyroid-stimulating hormone (TSH) concentrations in females with marginal significance ($\beta = 0.066$, $p = 0.058$). However, no significant association was identified between triclosan exposure and serum total triiodothyronine and thyroxine in both males and females, and TSH in males.

Conclusions: This study is the first human study to evaluate the relationship between triclosan exposure and serum thyroid hormone concentrations in the Korean population. There was suggestive positive association between triclosan exposure and the serum TSH in females. Further studies need to evaluate the relationship between long-term exposure to low-dose triclosan and thyroid hormones.

Keywords: Endocrine-disrupting chemical; Triclosan; Thyroid hormone

BACKGROUND

5-chloro-2-(2,4-dichlorophenoxy)phenol (triclosan) is a synthetic compound that has broad antimicrobial action. It is used as an antiseptic in personal hygiene products, such as soaps, body cleansers, hand sanitizers, deodorants, and cosmetics, as well as in textiles, including carpets, socks, underwear, and sportswear [1-3]. With dermal application, 10% or less of the triclosan is absorbed into the body, while almost 100% is absorbed with oral ingestion [4]. Once in the body, triclosan is metabolized into glucuronide and sulfate conjugates and

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets analyzed during the current study are available on request at the National Institute of Environmental Research, Environmental Health Research Department, <http://www.nier.go.kr/NIER/kor/openapi/getAsub.do?menuNo=14010>.

Authors contributions

Formal analysis: Ha NY, Ryu JY; Funding acquisition: Ryu JY; Investigation: Kim DH; Supervision: Ryu JY; Writing - original draft: Ha NY, Ryu JY.

excreted mainly in urine [5]. The median excretion half-life of triclosan after oral intake in humans is 11 hours [6].

The toxic effects of triclosan have been studied. There have been several cases of contact dermatitis after using personal hygiene products containing triclosan, such as toothpaste and deodorant [7]. Triclosan may also increase the risk of allergy sensitization [8]. Some studies have suggested that triclosan is a potential endocrine-disrupting chemical that can affect estrogen, testosterone, and thyroid hormone levels [9-13]. In a cohort study, birth outcomes such as birth weight, length, head circumference, and gestational age were inversely related to maternal urinary triclosan levels [14].

Triclosan and thyroxine (T4) have similar molecular structures. Previous studies suggested that triclosan inhibits thyroid function because of this structural similarity [1,15]. A recent meta-analysis of rodent studies showed that the T4 concentration decreased in a dose-dependent manner with postnatal triclosan administration [13]. Triclosan decreased circulating serum total T4 [9,16-18] and total triiodothyronine (T3) [17] in rats. Compared to the animal studies that showed a distinct negative association between triclosan exposure and thyroid hormone levels, the results of previous human studies were inconsistent. A U.S. study found a positive association between triclosan and total T3 levels in adolescents [12]. There was a negative correlation between triclosan and serum free T4 in obese women [19]. In a study of pregnant women in the third trimester, triclosan levels were inversely associated with free T4 levels [20]. However, some studies did not show any significant relationship between triclosan exposure and thyroid function [21,22].

Although a few studies have evaluated the effects of triclosan exposure on thyroid function in humans, the results of these studies are inconsistent and, thus, the effect on thyroid hormones in human remains unclear. In this study, we investigated the relationship between triclosan exposure and thyroid hormones in Korean population.

METHODS

Study participants

Data from The Second Korean National Environmental Health Survey (KoNEHS), which was conducted by the National Institute of Environmental Research under the Ministry of Environment from 2012 to 2014, were analyzed. The survey examined 6,478 subjects from 400 districts who were selected through stratified multistage cluster sampling in proportion to the population distribution. Data were collected through personal interviews, physical examinations, and laboratory tests. We excluded subjects who were pregnant ($n = 30$) or had thyroid diseases ($n = 160$). Subjects with missing values ($n = 232$) or thyroid hormone extremes ($n = 66$) were also excluded. Finally, 5,990 subjects were included in the analysis.

Covariates

Age, sex, body mass index (BMI), and smoking status were included as variables. BMI was divided into 4 groups: underweight ($< 18.50 \text{ kg/m}^2$), normal ($18.50\text{--}22.99 \text{ kg/m}^2$), overweight ($23.00\text{--}24.99 \text{ kg/m}^2$), and obese ($\geq 25.00 \text{ kg/m}^2$). Smoking status was grouped into 2 conditions based on questionnaire: smoker and current non-smoker.

Triclosan exposure and urinary triclosan levels

Triclosan exposure was evaluated using urinary triclosan concentrations. Analytic method for urinary triclosan levels, which was detailed in KoNEHS laboratory manual, is as following. After spot urine specimens were collected, they were transferred to the laboratory in an ice box and stored frozen at -20°C until analysis. The urine samples were hydrolyzed with β -glucuronidase/aryl sulfatase and extracted with ethyl ether for measurement. The urinary triclosan concentrations were analyzed using ultra-performance liquid chromatography-mass spectrometry. The triclosan concentrations were determined using a calibration curve prepared by the standard addition method. The limit of detection (LOD) was $0.5\ \mu\text{g/L}$. The values below the LOD were treated with the LOD divided by the square root of 2.

Because 59.6% of the urinary triclosan concentrations were below the LOD, we classified triclosan into 2 groups: 'below detection ($< \text{LOD}$)' vs. 'detected ($\geq \text{LOD}$).'

Serum thyroid hormones

The thyroid profile measured included serum total T3, total T4, and thyroid-stimulating hormone (TSH or thyrotropin). Serum thyroid hormones were measured using chemiluminescence immunoassays (CLIA). Thyroid hormone concentrations were skewed and natural-log transformed before analysis.

Statistical analyses

Because the KoNEHS has been sampled by stratified multistage cluster method, a general linear model including stratum, cluster, and sample weights was used in analyses. The unweighted and weighted geometric mean of the serum total T3, total T4, and TSH and weighted percentage for urinary triclosan above the LOD were calculated according to the demographic characteristics. The serum thyroid hormone concentrations were compared with the t -test and ANOVA by demographic factors. The χ^2 test was used to analyze the difference in the proportions of detected triclosan exposure group by each variable. Multiple linear regression analysis was performed to determine the relationship between triclosan exposure (dichotomous variable: 'below detection' and 'detected') and serum thyroid hormone concentrations adjusting for age, BMI, urinary creatinine, and smoking status. SPSS (ver. 25; IBM, Armonk, NY, USA) was used for all statistical analyses.

Ethics statement

This study was approved by the Institutional Review Board of Haeundae Paik Hospital (IRB No. 2018-12-002).

RESULTS

Table 1 lists the geometric means and percentiles of serum thyroid hormone levels and urinary triclosan concentrations among the participants. The geometric means of serum total T3, total T4, and TSH were $98.55\ \text{ng/dL}$, $7.95\ \mu\text{g/dL}$, and $1.93\ \mu\text{IU/mL}$. The proportion of urinary triclosan concentrations below the LOD was 59.6% (61.6% in males and 58.1% in females). The geometric mean of urinary triclosan was not calculated. The 75th and 95th percentile of the urinary triclosan concentrations were $1.21\ \mu\text{g/L}$ and $41.73\ \mu\text{g/L}$, respectively.

Table 2 shows the geometric means of the serum thyroid hormone concentrations and percentages of urinary triclosan detection categorized by demographic characteristics.

Triclosan and thyroid hormones

Table 1. Distribution of serum thyroid hormone levels and urinary triclosan concentrations among the participants (n = 5,990)

Variable	% < LOD*	GM	Percentile							
			5th	10th	25th	50th	75th	90th	95th	
Total T3 (ng/dL)	0.0%									
Total		98.55	74.00	79.00	87.00	99.00	111.00	124.00	132.00	
Male		101.63	76.00	81.00	90.00	102.00	114.00	127.00	136.00	
Female		96.22	73.00	78.00	86.00	96.00	108.00	120.00	128.00	
Total T4 (µg/dL)	0.0%									
Total		7.95	5.70	6.30	7.10	8.10	9.00	9.90	10.40	
Male		7.93	5.60	6.20	7.10	8.10	9.00	9.89	10.40	
Female		7.96	5.70	6.30	7.20	8.10	9.00	9.90	10.40	
TSH (µIU/mL)	0.0%									
Total		1.93	0.66	0.86	1.29	1.95	2.92	4.29	5.43	
Male		1.81	0.64	0.81	1.20	1.83	2.74	3.96	4.92	
Female		2.03	0.69	0.91	1.36	2.04	3.05	4.56	5.77	
Triclosan (µg/L)										
Total	59.6%	NC	-	-	-	-	1.21	7.89	41.73	
Male	61.6%	NC	-	-	-	-	1.10	6.37	41.29	
Female	58.1%	NC	-	-	-	-	1.34	9.25	42.89	

LOD: limit of detection; GM: geometric mean; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; Triclosan: 5-chloro-2-(2,4-dichlorophenoxy)phenol; NC: not calculated; -, below limit of detection.

*LOD = 0.5 µg/L.

Table 2. Geometric mean with 95% CI of serum thyroid hormone levels and percentage for urinary triclosan above the detection limit by demographic characteristics

Variable	Category	No. (weighted %)	Total T3 (ng/dL)		Total T4 (µg/dL)		TSH (µIU/mL)		Triclosan detected*
			Unweighted GM (95% CI)	Weighted GM (95% CI)	Unweighted GM (95% CI)	Weighted GM (95% CI)	Unweighted GM (95% CI)	Weighted GM (95% CI)	No. (weighted %)
Sex	Male	2,630 (50.3)	101.63 (100.93–102.32)	102.08 (100.91–103.28)	7.93 (7.88–7.99)	7.96 (7.88–8.04)	1.81 (1.76–1.85)	1.77 (1.72–1.82)	1,010 (41.5)
	Female	3,360 (49.7)	96.22 (95.65–96.79)	95.62 (94.60–96.64)	7.96 (7.91–8.01)	7.96 (7.88–8.04)	2.03 (1.98–2.07)	1.96 (1.91–2.02)	1,409 (43.9)
	<i>p</i> -value		< 0.001	< 0.001	0.534	0.991	< 0.001	< 0.001	0.158
Age (years)	19–29	499 (17.7)	98.36 (96.88–99.84) [†]	98.35 (96.38–100.35)	8.01 (7.88–8.15)	7.98 (7.82–8.14)	1.53 (1.46–1.62) [†]	1.53 (1.45–1.62) [†]	255 (49.4)
	30–39	981 (20.0)	98.06 (96.95–99.19) [†]	99.13 (97.43–100.87)	7.93 (7.84–8.01)	7.97 (7.85–8.09)	1.82 (1.75–1.88) [†]	1.77 (1.69–1.85) [†]	422 (43.8)
	40–49	1,153 (21.5)	98.47 (97.50–99.46) [†]	98.35 (96.71–100.00)	7.94 (7.86–8.02)	7.96 (7.84–8.07)	1.97 (1.90–2.04) [†]	1.94 (1.86–2.02) [§]	508 (45.1)
	50–59	1,325 (19.3)	99.49 (98.53–100.47) [†]	100.33 (98.95–101.74)	7.90 (7.82–7.98)	7.92 (7.81–8.03)	2.04 (1.97–2.12) [§]	2.03 (1.93–2.13) [§]	549 (42.9)
	60–69	1,232 (11.0)	99.67 (98.67–100.69) [†]	98.98 (97.43–100.55)	7.99 (7.90–8.08)	7.95 (7.83–8.07)	2.00 (1.93–2.08) [§]	2.05 (1.95–2.15) [§]	435 (35.5)
	≥ 70	800 (10.4)	96.14 (94.94–97.36) [†]	97.03 (95.28–98.81)	7.94 (7.83–8.04)	7.98 (7.84–8.12)	1.98 (1.88–2.08) [§]	2.05 (1.92–2.18) [§]	250 (31.6)
	<i>p</i> -value		< 0.001	0.073	0.629	0.985	< 0.001	< 0.001	< 0.001
<i>p</i> for trend			0.331	0.794	0.616	0.766	< 0.001	< 0.001	
BMI (kg/m ²)	< 18.50	142 (3.0)	93.51 (90.41–96.72) [†]	93.07 (89.26–97.04) [†]	8.01 (7.75–8.28)	8.19 (7.88–8.51)	1.58 (1.42–1.75) [†]	1.44 (1.26–1.63) [†]	58 (40.9)
	18.50–22.99	2,040 (36.4)	95.51 (94.77–96.24) [†]	95.71 (94.57–96.85) [†]	7.95 (7.89–8.01)	7.93 (7.83–8.02)	1.84 (1.79–1.90) [†]	1.80 (1.74–1.86) [†]	832 (42.4)
	23.00–24.99	1,491 (23.1)	98.67 (97.81–99.53) [†]	99.08 (97.72–100.45) [†]	7.89 (7.82–7.97)	7.90 (7.79–8.01)	1.96 (1.90–2.03) [†]	1.86 (1.79–1.93) [†]	606 (43.3)
	≥ 25.00	2,317 (37.5)	101.57 (100.83–102.31) [§]	102.26 (101.00–103.53) [§]	7.97 (7.91–8.03)	8.01 (7.92–8.10)	2.00 (1.95–2.06) [†]	1.97 (1.91–2.04) [§]	923 (42.8)
	<i>p</i> -value		< 0.001	< 0.001	0.403	0.088	< 0.001	< 0.001	0.962
<i>p</i> for trend			< 0.001	< 0.001	0.656	0.480	< 0.001	< 0.001	
Smoking status	Smoker	1,090 (22.0)	104.19 (103.06–105.33)	104.57 (102.87–106.31)	8.09 (8.00–8.18)	8.10 (7.98–8.21)	1.60 (1.54–1.65)	1.60 (1.53–1.67)	408 (40.7)
	Current	4,900 (78.0)	97.34 (96.86–97.82)	97.25 (96.27–98.23)	7.91 (7.87–7.95)	7.92 (7.84–7.99)	2.01 (1.97–2.05)	1.95 (1.90–1.99)	2,011 (43.3)
	non-smoker								
<i>p</i> -value		< 0.001	< 0.001	< 0.001	0.003	< 0.001	< 0.001	0.230	
Total		5,990 (100)	98.55 (98.11–99.00)	98.82 (97.83–99.81)	7.95 (7.91–7.98)	7.96 (7.89–8.03)	1.93 (1.89–1.96)	1.86 (1.83–1.90)	2,419 (42.7)

BMI: body mass index; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; Triclosan: 5-chloro-2-(2,4-dichlorophenoxy)phenol; GM: geometric mean; CI: confidence interval; LOD: limit of detection.

*Sample size and weighted percentage for urinary triclosan above the detection limit (≥ LOD, 0.5 µg/L); Post hoc analysis ([†] < [‡] < [§]).

In females, the total T3 concentration was significantly lower ($p < 0.001$) and the TSH concentration was significantly higher ($p < 0.001$) than in males. The geometric mean of TSH increased with age (p for trend < 0.001). The geometric mean of total T3 (p for trend < 0.001) and the geometric mean of TSH (p for trend < 0.001) were significantly higher as BMI increased. The smoker group had a significantly higher geometric mean of total T3 ($p < 0.001$) and total T4 ($p = 0.003$), and lower geometric mean of TSH ($p < 0.001$) than the current non-smoker group.

Table 3. Weighted adjusted* regression coefficients and estimated mean with 95% CI between serum thyroid hormones and triclosan exposure group†

Triclosan exposure group	In total T3 (ng/dL)	Total T3 (ng/dL)	In total T4 (µg/dL)	Total T4 (µg/dL)	In TSH (µIU/mL)	TSH (µIU/mL)
	β (95% CI)	Estimated mean (95% CI)	β (95% CI)	Estimated mean (95% CI)	β (95% CI)	Estimated mean (95% CI)
Male						
Detected (≥ LOD‡)	0.000 (−0.019, 0.018)	103.11 (101.36, 104.88)	−0.011 (−0.033, 0.010)	7.95 (7.82, 8.08)	0.028 (−0.035, 0.091)	1.76 (1.68, 1.85)
Below detection (< LOD)	0 (reference)	103.13 (101.85, 104.43)	0 (reference)	8.04 (7.94, 8.15)	0 (reference)	1.71 (1.65, 1.78)
p-value	0.984		0.298		0.379	
Female						
Detected (≥ LOD)	−0.010 (−0.028, 0.007)	94.79 (92.02, 97.64)	−0.010 (−0.028, 0.008)	7.93 (7.70, 8.16)	0.066 (−0.002, 0.134)	1.86 (1.71, 2.02)
Below detection (< LOD)	0 (reference)	95.78 (92.82, 98.84)	0 (reference)	8.01 (7.80, 8.22)	0 (reference)	1.74 (1.60, 1.89)
p-value	0.251		0.288		0.058	

T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; Triclosan: 5-chloro-2-(2,4-dichlorophenoxy)phenol; CI: confidence interval; LOD: limit of detection.

*Adjusted for age, body mass index, urinary creatinine, and smoking status; †Coded as a dichotomous variable, regression coefficient represents change in serum thyroid measure in relation to having a detectable urinary triclosan concentration; ‡LOD = 0.5 µg/L.

Table 3 describes the results of the multiple linear regression analysis using dichotomous variables adjusting for age, BMI, urinary creatinine, and smoking status. When grouped by sex, detection of triclosan was positively associated with the serum TSH concentrations in females with marginal significance ($\beta = 0.066$, $p = 0.058$). However, no significant association was identified between triclosan exposure and serum total T3 and T4 in both males and females, and TSH in males.

DISCUSSION

This study assessed the relationship between triclosan exposure and thyroid hormones in the Korean population. In this study, there was suggestive positive association between triclosan exposure and the serum TSH in females, but not in males. There was no statistically significant association between triclosan exposure and serum total T3 and T4 in both males and females.

In a meta-analysis of rodent studies, the T4 concentration decreased in a dose-dependent manner with postnatal triclosan administration [13]. In several in vivo studies of adult rats, triclosan increased the elimination of thyroid hormone via hepatic catabolism, causing decreases in the serum T4 and T3 concentrations, with increased T4 glucuronidation and upregulation of phase II enzymes in the liver [17,23]. In other in vitro and in vivo studies, triclosan also affected thyroid hormone metabolism by inhibiting sulfotransferase or deiodinase activity, which plays an important role in thyroid hormone synthesis [24-26].

While animal studies have shown that there is a distinct association between triclosan and thyroid hormone levels, the results of human studies evaluating the relationship between triclosan and thyroid hormones have shown conflicting findings. In a study of U.S. population, triclosan exposure and total T3 concentrations were positively associated in adolescents [12]. On the other hand, several studies have found that the thyroid function may be hindered by triclosan. There was a negative association of urinary triclosan with serum free T4 in obese women [19] and urinary triclosan levels were negatively correlated with the serum free T4 in the pregnant women of the third trimester [20]. In a prospective preconception cohort, there was an inverse relationship between urinary triclosan concentrations and serum free T3 among women [27]. In another cohort study of pregnant women, urinary triclosan had a significant association with a decrease in total T3 [28].

However, some studies did not show statistically significant outcomes between triclosan exposure and thyroid function. There was no significant difference in thyroid function in patients with coronary heart disease using 0.3% triclosan toothpaste for more than 4 years compared with a control group [21]. Random intervention of personal hygiene products (e.g., toothpaste and soap) containing a triclosan in pregnant women showed no significant results in thyroid function during pregnancy or in the body measurements of babies at delivery [22].

The finding of our study is not consistent with the previous researches, but it also suggests that triclosan may have an effect that interferes with thyroid function. Our study showed a positive association between triclosan exposure and serum TSH concentrations in females with marginal significance. This might be due to the negative feedback of serum free T4, which was not included in KoNEHS, although there were no significant correlations between triclosan exposure and the serum total T4 or T3.

Previous animal studies have shown that triclosan has a significant effect on thyroid hormones. However, in this study, there was a suggestive association with TSH among females only. This result appears to be related to the difference in the triclosan exposure level. Animal studies identified the effects of high-dose triclosan exposure on thyroid hormones, while the level of triclosan exposure in the current study is considered to be low. The 95th percentile of the urinary triclosan concentrations among the participants in current study was 41.73 µg/L. The German Human Biomonitoring Commission has stated that there is no risk of adverse health effects on the human body with up to 3,000 µg/L of urinary triclosan for adults based on animal study [29]. Nevertheless, it is necessary to evaluate the effect of long-term exposure to low-concentration of triclosan on thyroid hormone levels.

In our study, the proportion of urinary triclosan concentrations which was below the LOD among the participants was 59.6%. The 75th and 95th percentile of the urinary triclosan concentrations among the study population were 1.21 µg/L and 41.73 µg/L. The detection rate and the 75th and 95th percentile concentrations were highly low compared with U.S. and Canada data [30,31]. This may be related to the difference in overall national consumption of personal hygiene products containing triclosan, such as toothpaste, soap, body cleanser, hand sanitizer, and deodorant. When a product containing triclosan is used, triclosan can be rapidly absorbed into the skin or into the mucous membrane of the mouth and excreted mainly in urine [4,5]. Therefore, if products containing triclosan are frequently used, the detection rate of triclosan in urine can also increase.

This is the first human study to assess the relationship between triclosan exposure and thyroid hormones in the Korean population. The few reported human studies have produced inconsistent results. In addition to the previous studies, our study provides data on the effect of triclosan exposure on thyroid hormones. However, there are some limitations in our study. First, the serum free T4 concentrations, which are used to evaluate essential thyroid functions and diagnose thyroid diseases, were not included in the laboratory tests. We could not evaluate the relationship between serum free T4 and triclosan exposure. Second, the long-term effect of triclosan exposure on thyroid hormones could not be identified because KoNEHS is a cross-sectional observational study. Third, spot urine specimens were collected in this study. A single urine sample of triclosan might not be representative of the subject's body burden due to the short half-life of triclosan. However, Smith et al. [32] suggested that a single urine specimen may reasonably indicate an individual's exposure over several months.

Thyroid hormones play an important role in human metabolism and normal fetal development. In Korea, triclosan was banned in the domestic market for toothpastes and mouthwashes in 2015. However, triclosan can still be used in other household products, such as antimicrobial wash products, plastics, and fibers. Therefore, further studies need to evaluate the relationship between long-term exposure to low-dose triclosan and thyroid hormones. Because the survey used in this study was conducted before triclosan was banned in 2015, further studies using the third KoNEHS (2015–2017) are also required.

CONCLUSIONS

This study was the first to evaluate the relationship between triclosan exposure and serum thyroid hormone concentrations in the Korean population. There was suggestive positive association between triclosan exposure and the serum TSH in females. Further studies that complement the limitations of this study are needed.

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