JES

JOURNAL OF
ENVIRONMENTAL
SCIENCES

www.jesc.ac.cn

ELSEVIER

Urinary concentrations of phenols, oxidative stress biomarkers and thyroid cancer: Exploring associations and mediation effects

Pan-Pan Chen [1,2], Pan Yang [3], Chong Liu [1,2], Yan-Ling Deng [1,2], Qiong Luo [1,2], Yu Miao [1,2], Min Zhang [1,2], Fei-Peng Cui [1,2], Jia-Yue Zeng [1,2], Tian Shi [1,2], Ting-Ting Lu [1,2], Da Chen [4], Long-Qiang Wang [5], Chun-Ping Liu [6,*], Ming Jiang [5,*], Qiang Zeng [1,2,*]

[1] Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[2] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health (incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030 , China
[3] Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou 510632, China
[4] School of Environment, Guangdong Key Laboratory of Environmental Pollution and Health, Jinan University, Guangzhou 510632, China
[5] Department of Thyroid and Breast Surgery, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[6] Department of Thyroid and Breast Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China

ARTICLE INFO

ABSTRACT

Phenols have been shown to influence the cellular proliferation and function of thyroid in experimental models. However, few human studies have investigated the association between phenol exposure and thyroid cancer, and the underlying mechanisms are also poorly understood. We conducted a case-control study by age- and sex-matching 143 thyroid cancer and 224 controls to investigate the associations between phenol exposures and the risk of thyroid cancer, and further to explore the mediating role of oxidative stress. We found that elevated urinary triclosan (TCS), bisphenol A (BPA) and bisphenol S (BPS) levels were associated with increased risk of thyroid cancer (all P for trends < 0.05), and the adjusted odds ratios (ORs) comparing the extreme exposure groups were 3.52 (95% confidence interval (CI): 2.08, 5.95), 2.06 (95% CI: 1.06, 3.97) and 7.15 (95% CI: 3.12, 16.40), respectively. Positive associations were also observed between urinary TCS, BPA and BPS and three oxidative stress biomarkers measured by 8-hydroxy-2′-deoxyguanosine (8-OHdG), 8-iso-prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$) and 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA), as well as between uri-

* Corresponding authors.
  E-mails: lcp191@163.com (C.-P. Liu), jm0911@sina.com (M. Jiang), zengqiang506@163.com (Q. Zeng).

nary 8-isoPGF$_{2\alpha}$ and HNE-MA and the risk of thyroid cancer. Mediation analysis showed that urinary 8-isoPGF$_{2\alpha}$ mediated 28.95%, 47.06% and 31.08% of the associations between TCS, BPA and BPS exposures and the risk of thyroid cancer, respectively (all $P < 0.05$). Our results suggest that exposure to TCS, BPA and BPS may be associated with increased risk of thyroid cancer and lipid peroxidation may be an intermediate mechanism. Further studies are warranted to confirm the findings.

Introduction

Thyroid cancer has been a worldwide health concern due to its increasing incidence in the past several decades (Li et al., 2020). It was estimated that more than 586,000 new cases of diagnosed thyroid cancer have been identified around the world in 2020 and accounts for 3% of the worldwide incidence of all cancers (Miranda-Filho et al., 2021). In China, an increasing trend of thyroid cancer incidence has also been reported, with the age-adjusted incidence rising from 3.21/100,000 in 2005 to 9.61/100,000 in 2015 (Wang et al., 2020). The etiology of thyroid cancer is multifactorial and largely not known. To date, only radiation exposure has been recognized as a well-known risk factor of thyroid cancer. Recently, increasing evidence has shown that exposure to certain endocrine-disrupting chemicals may contribute to the development of thyroid malignancy (Lerro et al., 2021; Liu et al., 2020; Marotta et al., 2019).

Phenol compounds, including triclosan (TCS), bisphenol A (BPA), and its substitutes are known as endocrine disruptors, which can disturb estrogen and/or androgen activities or bind to thyroid hormone receptors and further lead to a series of adverse health effects including thyroid dysfunction (Petrakis et al., 2017). Human can be constantly exposed to phenols through ingestion of food and drinking water, or through dermal contact with personal care products (Chen et al., 2016). Existing *in vivo* and *in vitro* studies have shown that TCS, BPA and its substitutes, such as bisphenol F (BPF) and bisphenol S (BPS), can impair the thyroid function, manifested by altering thyroid volume and structure, disrupting thyroid hormone levels, and even promoting the proliferation of thyroid tumor cells (Axelstad et al., 2013; da Silva et al., 2019; Fernandez et al., 2018; Hinther et al., 2011; Jiang et al., 2016; Lee et al., 2019; Sauer et al., 2021; Zhang et al., 2017). However, epidemiological studies exploring the association between phenol exposure and the risk of thyroid cancer are limited. To the best of our knowledge, only two previous studies found that urinary BPA and bisphenol AF (BPAF) concentrations were positively associated with the risk of thyroid cancer. However, their findings should be interpreted with caution due to the limited sample size ($n < 60$) (Marotta et al., 2019; Zhou et al., 2017).

Although existing evidence has suggested that phenol exposure may contribute to increased risk of thyroid cancer, the underlying mechanisms are poorly understood. Oxidative stress has been proposed as one of the mechanisms through which phenol exposure induces thyroid dysfunction (Gorini et al., 2020). Toxicological studies have shown that phenols, such as BPA, can impair oxidant/antioxidant balance and subsequently result in thyroid injury and thyroid hormone perturbation (Mohammed et al., 2020; Silva et al., 2018). Epidemiological evidence has also revealed that urinary concentrations of TCS, BPA and its substitutes (BPF and BPS) are positively associated with oxidative stress biomarkers including 8-iso-prostaglandin F$_{2\alpha}$ (8-isoPGF$_{2\alpha}$), 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) among healthy adult men (Wang et al., 2019), gestational women (Ferguson et al., 2019) and children (Lv et al., 2016). Furthermore, existing epidemiological studies have shown that elevated oxidative stress is associated with the occurrence of thyroid cancer (M Gerić, 2016; Wang et al., 2011). However, no human study to date has evaluated the potential mediation effect of oxidative stress on the association between phenol exposure and the risk of thyroid cancer.

In the present study, we performed a hospital-based case-control study to investigate the association between phenol exposure and the risk of thyroid cancer, and further explored the potential mediation effects by selected oxidative stress biomarkers. We measured urinary TCS, BPA, BPAF, BPF and BPS levels as indicators of phenol exposures, and urinary 8-OHdG, 8-isoPGF$_{2\alpha}$ and HNE-MA levels as oxidative stress biomarkers (Il'yasova et al., 2012).

1.   Methods and materials

1.1.   *Study participants*

The subjects of the study were recruited from a hospital in Wuhan, China during March to December 2016, as detailed in our prior study (Liu et al., 2020). In short, all participants in the case group were recruited before any treatment. After the surgery, a total of 144 subjects who were histologically diagnosed as thyroid cancer was included into the malignancy group. We excluded one subject who had insufficient urine volume for exposure measurements, resulting in 143 cases left in the malignancy group. People who came to the same hospital to seek for health examination were enrolled as the controls. After excluding those with thyroid diseases and certain occupational exposures (e.g., industrial solvents and polyvinyl chloride), 332 healthy people were recruited. Given that there are gender and age differences in thyroid cancer incidence, we sex and age-matched the controls with the cases by performing group matching. Finally, a total of 224 subjects were included in the control group. The Ethics Committee of Tongji Medical College approved our study, and each participant signed a written informed consent.

1.2. Basic information and urine collection

Information about basic demographic characteristics, smoking, alcohol consumption, radiation exposure, and medical history was collected from each subject through a face-to-face questionnaire. Nobody reported ever being exposed to ionizing irradiation. The smoking and drinking status were defined according to previous literature (Liu et al., 2020). The smokers were those who smoked "some days" or "everyday" and smoked more than 100 cigarettes throughout their lifetime, while ever-smokers were those who did not smoke currently but had smoked more than 100 cigarettes throughout their lifetime. The current-drinkers were those who consumed alcoholic beverages more than once per week. Before any medical treatment or surgery, one spot urine sample was collected from every participant in a sterile polypropylene cup. After collection, all the urine samples were shipped to the laboratory and kept at -20°C until detection.

1.3. Quantification of urinary phenols

Urinary phenols, including BPA, BPAF, BPS, BPF and TCS, were detected according to the method described elsewhere with minor modification (Wang et al., 2021; Wang et al., 2019). In brief, 0.5 mL of urine was added into a 15 mL of polypropylene tube. Upon addition of 200 μL of ammonium acetate buffer (1 mol/L, pH = 5.0) and 10 μL of β-glucuronidase from Helix pomatia, the sample was incubated at 37°C overnight for deconjugation. Then, 50 μL of mixed isotope-labeled standards (20 ng/mL) and 3 mL of methyl tert-butyl ether/ethyl acetate (5:1, V/V) were added to the sample and then centrifuged at 4,500 r/min for 10 min. The mixture was extracted three times with 3 mL of methyl tert-butyl ether/ethyl acetate (5:1; V/V). The final extract was concentrated to near dryness with a nitrogen, and then reconstructed with 100 μL of water (containing 60% acetonitrile) before instrumental analysis.

An Agilent ZORBAX Extend-C18 column (Narrow Bore RR 2.1 mm × 100 mm, 3.5-Micron, 80A) was used for the separation of target compounds. An ultraperformance liquid chromatography system coupled to an AB Sciex 5500 triple quadrupole mass spectrometry (MS/MS, Toronto, Canada) was used to determine the target chemicals. The mass spectrometer was equipped with an electron spray ionization probe in a negative mode and operated in the multiple reaction monitoring mode. A procedural blank and pooled urine samples spiked by the targets were run along with every batch to evaluate potential contamination and the efficiency of analytical procedure. The relative standard deviation and the average recoveries of the target analytes were in the ranges of 5.5%–19.5% and 71.6%–122.7%, respectively. The limit of detections (LODs) of phenols ranged from 0.01 to 0.08 ng/mL, which were calculated as a signal-to-noise ratio of 3. Phenol concentrations in all blank samples were all below the LODs. Values less than the LOD were replaced with LOD/$\sqrt{2}$ (Hornung and Reed, 1990).

1.4. Quantification of oxidative stress biomarkers

Urinary concentrations of oxidative stress biomarkers, including 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$, were measured by an established method as described previously (Wang et al., 2019). Briefly, a 100 μL urine supernatant was diluted with 1.5 mL deionized water and then spiked with 50 μL isotope-labeled standards (100 ng/mL). Oasis HLB cartridges were used to purify the mixture in the process of solid-phase extraction. The resulting eluent was evaporated to dryness and redissolved in 200 μL 5% methanol/water. The targets were separated by a Phenomenex Gemini-NX-C18 column (3 μm, 100 × 2 mm) in a high-performance liquid chromatograph and measured by an Agilent 6460 triple quadrupole mass spectrometer. The limit of quantifications (LOQs) of 8-OHdG, HNE-MA, and 8-isoPGF$_{2\alpha}$ were all less than 0.10 ng/mL. One blank (ultrapure water) and two pooled urine samples spiked with the targets were analyzed within each batch. The concentrations of analytes in all blank samples were below the LOQs; the recoveries of spiked specimens were from 87% to 102%. The average variations of inter- and intra-batch were all < 10%.

1.5. Determination of urinary creatinine

We determined urinary creatinine concentrations based on the Jaffe's colorimetric method with an automatic biochemical analyzer (Wang et al., 2015).

1.6. Statistical analysis

We used SPSS 25.0 and SAS 9.4 statistical software for the data analyses, and $P \leq 0.05$ was considered as statistically significant. Descriptive statistical analyses were performed for the characteristics of the study participants and the distribution of urinary phenols and oxidative stress biomarkers. Differences of categorical characteristics and continuous urinary phenols and oxidative stress biomarkers between the cases and controls were examined using the Chi-square tests and Mann-Whitney U tests, respectively. BPAF was excluded from further analysis due to its limited detection rate in urine samples.

Multivariate unconditional logistic regression models were conducted to explore the associations of urinary phenols and oxidative stress biomarkers with the risk of thyroid cancer. Multivariable linear regression models were applied to assess the associations of urinary phenols with oxidative stress biomarkers. BPS and all the oxidative stress biomarkers were categorized into tertiles according to the concentrations of the controls. Due to the limited detection rates of TCS and BPF, we dichotomized their concentrations into two groups by LOD (i.e., ≤LOD or >LOD). Considering the moderate detection rate of BPA, the values of BPA below the LOD were categorized into the lowest group, and the detectable values in the control group were evenly divided as the middle- and high-exposure groups. Urinary oxidative stress biomarkers were natural logarithm (ln) transformed to approximately achieve normality. The corresponding regression coefficients were back-transformed to get the percent changes according to the equation: {100 × [exp(beta) - 1]}. Tests for trends were conducted using integer values (0∼2) of three-level categorical variables or tertiles in the multivariate regression models. Urinary oxidative stress biomarkers modeled as continuous variables were also included in the multivariate regression models.

Statistical and biological factors were both taken into consideration in selection of potential covariates (Kwon et al., 2020; Liu et al., 2020). The potential covariates were included into the multivariate regression models when they resulted in > 10% changes in the estimated odds ratios (ORs) or regression coefficients. Finally, age (<30, 30–50 and ≥50, years), body mass index (BMI, <18.5, 18.5–24.9 and ≥24.9, kg/m^2) and household income (<713.5, 713.5–1427 and ≥1427, US\$/month) as three-category variables, gender (male vs. female), alcohol use (ever and current vs. never) and smoking status (ever and current vs. never) as dichotomous variables, and urinary creatinine as a continuous variable were included in the multivariate regression models (Barr et al., 2005).

To examine the mediating role of oxidative stress in the association between phenol exposure and the risk of thyroid cancer, we conducted the mediation analysis by SAS PROC CAUSALMED (SAS Institute Inc, 2020). The mediation analysis has been detailed elsewhere (Huang et al., 2020b; VanderWeele, 2013). When assumptions of the mediation analysis hold, the direct effect indicates the effect of phenol exposure on the risk of thyroid cancer after controlling for oxidative stress biomarkers, and the indirect effect is the estimated effect of phenol exposure on the risk of thyroid cancer through oxidative stress biomarkers. In the mediation analysis, the linear and logistic regression models were fitted as follows:

$$E[m|a, c] = \beta_0 + \beta_1 a + \beta_2' c$$

$$\text{logit}\{P(Y = 1|a, m, c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$$

In above equations, a is the exposure (phenols), m is the mediator (oxidative stress biomarkers), Y is the outcome (thyroid cancer) and c is the adjusted covariate. The factors adjusted in the mediation models were the same as those in the main analyses. The natural direct effect, natural indirect effect derived on the OR scale and the mediating proportion were all estimated by SAS PROC CAUSALMED.

2.   Results

Characteristics of the study participants are presented in **Table 1**. A majority of participants were females (71.9%) and only 6 participants were of not Han ethnicity. Most of subjects aged more than 30 years old (89.1%), had normal BMI ranges (69.4%), never smoked (82.6%) and drank alcohol (80.8%). The controls were more likely to have high education background and household income compared with the cases (both P-values < 0.01), but no other statistically significant differences in basic characteristics were observed between cases and controls (all P-values > 0.05).

Table 2 presents the distribution of urinary phenols and oxidative stress biomarkers. BPS and three oxidative stress biomarkers were detectable in nearly all the urine samples. More than half of the controls could be detected with BPA and BPF, and more than half of the cases could be detected with BPA and TCS, whereas the detection rates of BPAF in control and malignancy group were just 12.1% and 8.4%, respectively.

Compared with the control group, the case group had significantly higher concentrations of TCS, BPS and 8-isoPGF$_{2\alpha}$, whereas lower concentrations of BPF.

The associations of urinary phenols with the risk of thyroid cancer are presented in **Table 3**. The estimated ORs from crude models were similar to those from adjusted models. We observed monotonic dose-response associations between elevated BPA and BPS levels and increased risk of thyroid cancer in the adjusted models (P for trends =0.03 and <0.01, respectively). Compared to the reference group, the adjusted ORs were 2.09 [95% confidence interval (CI): 1.15, 3.77] and 2.06 (95% CI: 1.06, 3.97) for the middle- and high-exposure groups of BPA, respectively, and were 5.19 (95% CI: 2.28, 11.83) and 7.15 (95% CI: 3.12, 16.40) for the second and third tertiles of BPS, respectively. We also observed that participants with detectable TCS had an elevated risk of thyroid cancer (OR =3.52, 95% CI: 2.08, 5.95) compared with those with undetected values in the adjusted model. We found that subjects with detectable BPF had a decreased risk of thyroid cancer compared to those with undetected values in the crude model (OR =0.48, 95% CI: 0.30, 0.77), but the estimated OR in the adjusted model was not statistically significant (OR =0.61, 95% CI: 0.36, 1.03).

The crude and adjusted associations between urinary phenols and oxidative stress biomarkers among all the participants are similar (Appendix A **Table S1** and **Table 4**). After adjusting for relevant confounders, positive associations were observed across increasing BPA and BPS levels and 8-OHdG, 8-isoPGF$_{2\alpha}$ and HNE-MA, and across increasing TCS levels and 8-OHdG and 8-isoPGF$_{2\alpha}$, as well as across increasing BPF levels and 8-OHdG (all P for trends or P values <0.05). For example, 8-OHdG, 8-isoPGF$_{2\alpha}$ and HNE-MA increased by 21.29% (95% CI: 4.08%, 41.34%), 43.05% (95% CI: 17.94%, 73.67%) and 83.13% (95% CI: 32.98%, 151.93%) comparing the extreme BPA exposure groups, respectively. We did not observe statistically significant associations between TCS and HNE-MA, as well as between BPF and 8-isoPGF$_{2\alpha}$ and HNE-MA.

Table 5 shows the associations of urinary oxidative stress biomarkers with the risk of thyroid cancer. In both crude and adjusted models, positive dose-response associations were observed between elevated levels of 8-isoPGF$_{2\alpha}$ and HNE-MA and the risk of thyroid cancer. In comparison with those with the first tertiles of 8-isoPGF$_{2\alpha}$ and HNE-MA, subjects in the third tertiles had increased ORs of thyroid cancer in the adjusted models (OR =7.88; 95% CI: 3.81, 16.30 and OR =1.65; 95% CI: 0.92, 2.96, respectively). When 8-isoPGF$_{2\alpha}$ and HNE-MA were modeled as continuous variables, these relationships were still significant. In the adjusted models, one-unit increase in ln-transformed 8-isoPGF$_{2\alpha}$ and HNE-MA concentrations was associated with increased ORs of 3.65 (95% CI: 2.36, 5.63) and 1.23 (95% CI: 1.00, 1.52) in thyroid cancer, respectively. We did not find a statistically significant association between elevated tertiles of 8-OHdG and the risk of thyroid cancer, but found that continuous 8-OHdG was related to an increased OR of 1.57 (95% CI: 1.05, 2.35) in thyroid cancer in the crude model.

Because a potential mediator must be at least significantly related to both the exposure and the outcome (Valeri and Vanderweele, 2013), we investigated the mediating effects of 8-isoPGF$_{2\alpha}$ and HNE-MA on the associations between urinary TCS, BPA and BPS and the risk of thyroid cancer. We observed

Table 1 – Characteristics of the study population [n (%)].

Characteristics	Overall (n=367)	Control (n=224)	Malignancy (n=143)	P^a
Age (years)				
<30	40 (10.9)	23 (10.3)	17 (11.9)	0.70
30–50	161 (43.9)	102 (45.5)	59 (41.2)	
≥50	166 (45.2)	99 (44.2)	67 (46.9)	
Gender				
Female	264 (71.9)	161 (71.9)	103 (72.0)	0.98
Male	103 (28.1)	63 (28.1)	40 (28.0)	
Race				
Han	355 (98.3)	218 (97.8)	137 (99.3)	0.41
Other	6 (1.7)	5 (2.2)	1 (0.7)	
BMI (kg/m^2)				
<18.5	23 (6.4)	17 (7.7)	6 (4.3)	0.07
18.5–24.9	250 (69.4)	159 (71.9)	91 (65.5)	
≥25	87 (24.2)	45 (20.4)	42 (30.2)	
Education				
Less than high school	60 (16.5)	28 (12.7)	32 (22.5)	<0.01
High school	129 (35.5)	57 (25.8)	72 (50.7)	
College and above	174 (47.9)	136 (61.5)	38 (26.8)	
Household income (US$/month)				
<713.5	114 (31.9)	56 (25.1)	58 (43.3)	<0.01
713.5–1427	139 (38.9)	82 (36.8)	57 (42.5)	
≥1427	104 (29.1)	85 (38.1)	19 (14.2)	
Smoking status				
Never	294 (82.6)	183 (81.7)	111 (84.1)	0.57
Ever and current	62 (17.4)	41 (18.3)	21 (15.9)	
Alcohol use				
Never	287 (80.8)	183 (82.4)	104 (78.2)	0.33
Ever and current	68 (19.2)	39 (17.6)	29 (21.8)	

   ᵃ P-values indicate the differences between the control and thyroid malignancy groups.

Table 2 – Distribution of urinary phenols and oxidative stress biomarkers in study population

Compounds (µg/L)	Control			Malignancy			P^a
	DR (%)	Median	25th–75th	DR (%)	Median	25th–75th	
TCS	31.9	<LOD	<LOD–0.74	62.2	0.93	<LOD–7.60	<0.01
BPA	64.3	1.25	<LOD–2.18	67.8	1.04	<LOD–1.98	0.97
BPAF	12.1	–	–	8.4	–	–	0.27
BPF	61.2	1.24	<LOD–3.29	35.7	<LOD	<LOD–1.30	<0.01
BPS	99.1	0.67	0.36–1.18	100.0	0.83	0.63–1.30	<0.01
8-OHdG	100.0	7.10	4.34–10.20	100.0	5.68	3.92–8.44	0.06
8-isoPGF$_{2\alpha}$	100.0	5.29	3.27–7.99	100.0	7.07	4.04–10.99	<0.01
HNE-MA	100.0	18.85	10.96–32.67	100.0	27.66	7.05–64.69	0.11

DR, detection rate; TCS, triclosan; BPA, bisphenol A; BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; 8-isoPGF$_{2\alpha}$, 8-iso-prostaglandin F$_{2\alpha}$; HNE-MA, 4-hydroxy-2-nonenal-mercapturic acid.
   ᵃ P-values indicate the differences between the control and thyroid malignancy groups

that urinary TCS, BPA and BPS had statistically significant indirect effects on the risk of thyroid cancer through increased urinary 8-isoPGF$_{2\alpha}$, and the estimated ORs were 1.28 (95% CI: 1.02, 1.54) for TCS, 1.09 (95% CI: 1.03, 1.15) for BPA and 1.17 (95% CI: 1.05, 1.30) for BPS (**Fig. 1**). The mediation proportion of 8-isoPGF$_{2\alpha}$ on the relationships of urinary TCS, BPA and BPS with the risk of thyroid cancer were 28.95%, 47.06% and 31.08%, respectively (all P values < 0.05, **Fig. 1**). When regarding HNE-MA as a mediator of the associations between BPA and BPS and the

risk of thyroid cancer, the indirect effects were not statistically significant (Appendix A **Fig. S1**).

3. Discussion

In this hospital-based case-control study in Wuhan, China, three urinary phenols (TCS, BPA and BPS) and two urinary oxidative stress biomarkers (8-isoPGF$_{2\alpha}$ and HNE-MA) were

Table 3 – Crude and adjusted ORs for the risk of thyroid cancer in relation to urinary phenols in the study population.

Phenols (μg/L)	Cases/Controls	OR (95% CI)	
		Crude Model[a]	Adjusted Model[b]
TCS			
≤LOD	54/139	ref	ref
>LOD	89/85	3.74 (2.32, 6.01)	3.52 (2.08, 5.95)
P-value		<0.01	<0.01
BPA			
≤LOD	46/80	ref	ref
0.04–1.84	57/72	1.78 (1.05, 3.02)	2.09 (1.15, 3.77)
1.84–26.03	40/72	1.75 (0.97, 3.17)	2.06 (1.06, 3.97)
P for trend		0.05	0.03
BPF			
≤LOD	92/87	ref	ref
>LOD	51/137	0.48 (0.30, 0.77)	0.61 (0.36, 1.03)
P-value		<0.01	0.07
BPS			
T1 (0.04–0.45)	9/75	ref	ref
T2 (0.45–0.97)	73/75	7.81 (3.59, 17.02)	5.19 (2.28, 11.83)
T3 (0.97–67.96)	61/74	8.18 (3.69, 18.13)	7.15 (3.12, 16.40)
P for trend		<0.01	<0.01

OR, odds ratio; CI, confidence interval; ref, reference; TCS, triclosan; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S.

[a] The model was adjusted for urinary creatinine.
[b] The model was adjusted for urinary creatinine, gender, age, BMI, alcohol use, smoking status and income.

Table 4 – Percent changes (95% CI) for urinary oxidative stress biomarkers in relation to urinary phenols among study participants.[a]

Phenols (μg/L)	Percent changes (95% CI)		
	8-OHdG[b]	8-isoPGF$_{2\alpha}$[b]	HNE-MA[b]
TCS			
≤LOD	ref	ref	ref
>LOD	14.68 (1.92, 29.18)	21.65 (4.71, 41.34)	11.63 (-13.15, 43.48)
P-value	0.02	0.01	0.39
BPA			
≤LOD	ref	ref	ref
0.04–1.84	22.38 (6.40, 40.78)	17.00 (-1.88, 39.51)	53.88 (15.03, 105.85)
1.84–26.03	21.29 (4.08, 41.34)	43.05 (17.94, 73.67)	83.13 (32.98, 151.93)
P for trend	0.01	<0.01	<0.01
BPF			
≤LOD	ref	ref	ref
>LOD	24.61 (9.75, 41.34)	14.57 (-2.66, 34.72)	0.40 (-23.43, 31.65)
P-value	<0.01	0.10	0.98
BPS			
T1 (0.04–0.50)	ref	ref	ref
T2 (0.50–0.92)	32.05 (13.31, 54.03)	29.95 (6.72, 58.09)	13.09 (-18.62, 57.15)
T3 (0.92–67.96)	37.85 (18.77, 60.00)	41.20 (16.77, 70.92)	46.92 (5.23, 99.37)
P for trend	<0.01	<0.01	0.02

CI, confidence interval; ref, reference; TCS, triclosan; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; 8-isoPGF$_{2\alpha}$, 8-iso-prostaglandin F$_{2\alpha}$; HNE-MA, 4-hydroxy-2-nonenal-mercapturic acid

[a] The model was adjusted for urinary creatinine, gender, age, BMI, alcohol use, smoking status and income.
[b] The values were transformed by the natural logarithm and back-transformed to obtain the percent changes

proved to be related to increased risk of thyroid cancer. Moreover, we observed that TCS, BPA and BPS were associated with increased oxidative stress status manifested as elevated urinary 8-OHdG, 8-isoPGF$_{2\alpha}$ and HNE-MA concentrations. Mediation analysis further suggested that urinary 8-isoPGF$_{2\alpha}$ me-

diated part of the positive associations between TCS, BPA, BPS exposures and the risk of thyroid cancer.

Among the measured phenols, BPS had the highest detection rate, followed by BPA, and BPF had higher detection rate in the control group than that in the cancer group, suggesting

Table 5 – Crude and adjusted ORs for the risk of thyroid cancer in relation to urinary oxidative stress biomarkers in the study population

Oxidative stress biomarkers (µg/L)	Cases/Controls	OR (95% CI)	
		Crude Model[a]	Adjusted Model[b]
8-OHdG			
T1 (0.41–4.99)	57/75	ref	ref
T2 (4.99–9.09)	58/75	1.45 (0.86, 2.45)	1.22 (0.68, 2.19)
T3 (9.09–45.52)	28/74	1.06 (0.55, 2.05)	0.86 (0.41, 1.82)
P for trend		0.70	0.81
Continuous[c]		1.57 (1.05, 2.35)	1.57 (0.99, 2.50)
8-isoPGF$_{2\alpha}$			
T1 (0.57–3.84)	32/75	ref	ref
T2 (3.84–6.87)	38/75	1.82 (0.99, 3.33)	1.70 (0.84, 3.46)
T3 (6.87–126.64)	73/74	6.56 (3.42, 12.56)	7.88 (3.81, 16.30)
P for trend		<0.01	<0.01
Continuous[c]		3.30 (2.24, 4.86)	3.65 (2.36, 5.63)
HNE-MA			
T1 (0.47–12.63)	55/75	ref	ref
T2 (12.63–26.19)	15/75	0.39 (0.20, 0.76)	0.36 (0.17, 0.75)
T3 (26.19–1057.88)	73/74	2.05 (1.22, 3.44)	1.65 (0.92, 2.96)
P for trend		<0.01	0.06
Continuous[c]		1.31 (1.08, 1.57)	1.23 (1.00, 1.52)

OR, odds ratio; CI, confidence interval; ref, reference group; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; 8-isoPGF$_{2\alpha}$, 8-iso-prostaglandin F$_{2\alpha}$; HNE-MA, 4-hydroxy-2-nonenal-mercapturic acid

[a] The model was adjusted for urinary creatinine

[b] The model was adjusted for urinary creatinine, gender, age, BMI, alcohol use, smoking status and income.

[c] The values were transformed using the natural logarithm.

the widespread use of BPA substitutes. Recent studies have shown that there are increasing trends on urinary concentrations of BPA substitutes such as BPA and BPF (Hu et al., 2019). Higher median concentrations of TCS and BPS were also observed in the cancer group compared with the control group. The lower education level and household income in the cancer group may be responsible for the discrepancy. Several studies have reported that lower education level and household income are associated with higher urinary phenol concentrations (Casas et al., 2013; Cui et al., 2021). In addition, different dietary habits may play important roles in the variation of exposure to phenols between two groups (Smith et al., 2012).

Toxicological evidence has demonstrated that phenols can induce cellular proliferation and dysfunction of thyroid. An *in vitro* study found that low levels of BPA (1 mmol/L–10 nmol/L) could stimulate proliferation of human thyroid tumor cells (Zhang et al., 2017). BPA at a concentration compatible with human exposed levels (10^{-7} mol/L) was also demonstrated to facilitate the progression of papillary thyroid cancers harboring $BRAF^{V600E}$ mutation by promoting epithelial-mesenchymal transition in both clinical investigation and cultured thyroid cells (Li et al., 2021). In addition, mounting evidence has shown that exposure to BPA, BPF, BPS and TCS disrupt thyroid hormone homeostasis, which may contribute to the progression of thyroid cancer (Farasani and Darbre, 2020; Paul et al., 2012; Wu et al., 2016; Zhang et al., 2018).

To our knowledge, only two epidemiological studies have investigated the associations between phenol exposures and thyroid cancer (Marotta et al., 2019; Zhou et al., 2017). In agreement with our results, Zhou et al. (2017) found that the geometric mean concentrations of urinary BPA were higher in

papillary thyroid carcinoma (*n* =53) than those in health control group (*n* =65), and subjects with higher urinary BPA concentrations (>2.84 µg/L) had a 3.57-fold increased risk of papillary thyroid carcinoma. However, a cross-sectional study (*n* =55 in total) in Italy did not find any significant associations between BPA, BPS and BPF measured in serum and the risk of differentiated thyroid cancer, but found an increased risk for BPAF (OR =15.07; 95% CI: 1.59, 142.13) (Marotta et al., 2019). Our results were not directly comparable to this study as they used the patients with benign thyroid nodules as the controls. In addition, the exposure biomarkers measured in different biological matrix and different sample sizes may contribute to the inconsistent results between studies. The low detection rate of urinary BPAF in our study also limited our further estimation with the risk of thyroid cancer.

Numerous *in vivo* and *in vitro* studies have shown that exposure to TCS, BPA and its analogues (BPAF, BPF and BPS) can induce oxidative stress, manifested as the generation of reactive oxygen species, increased lipid peroxidation, and decreased antioxidant capacity (An et al., 2020; Gomes et al., 2020; Huang et al., 2020a; Mukherjee et al., 2020; Qiu et al., 2019; Ullah et al., 2019). Consistent with these experimental results, a variety of human studies have also reported positive associations between urinary TCS, BPA and BPS and oxidative stress biomarkers such as 8-OHdG, 8-isoPGF$_{2\alpha}$ and HNE-MA among different populations (Ferguson et al., 2019; Wang et al., 2019; Zhang et al., 2016). Specifically, our previous study found that urinary BPA and BPF were related to elevated urinary levels of 8-OHdG, 8-isoPGF$_{2\alpha}$ and HNE-MA in adult men (Wang et al., 2019). Ferguson et al. (2019) also found that urinary BPS and TCS concentrations were associated with
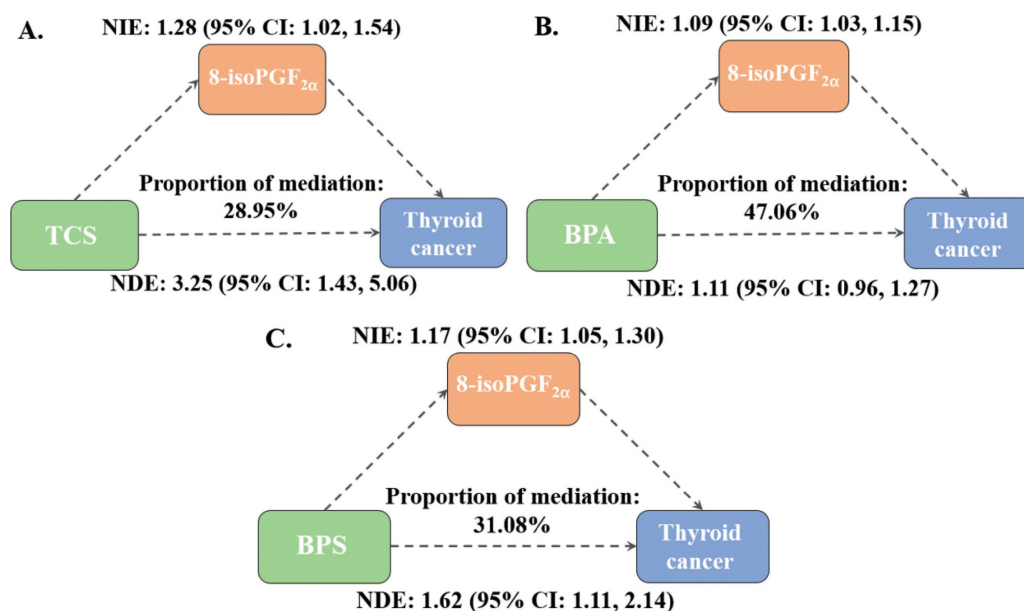
Fig. 1 – Mediation effects investigating whether oxidative stress mediates the associations between phenol exposures and the risk of thyroid cancer. The natural direct effect (NDE), natural indirect effect (NIE) and the mediating proportion were estimated by SAS PROC CAUSALMED. The models were adjusted for urinary creatinine, gender, age, BMI, alcohol use, smoking status and income.

increased urinary 8-OHdG and 8-isoPGF$_{2\alpha}$ levels among pregnant women from Boston.

It is well-known that oxidative stress is an important contributor to the formation and progression of cancer (Klaunig, 2018). A previous human study found that the levels of lipid peroxidation (4-HNE) and DNA damage (8-oxo-dG) were significantly higher in benign and malignant thyroid neoplasia than those of normal thyroid tissue (Young et al., 2010). In the current study, positive relationships were exhibited between lipid peroxidation, as reflected by 8-isoPGF$_{2\alpha}$ and HNE-MA, and the increased risk of thyroid cancer. Consistent with our findings, several researches revealed that patients diagnosed with thyroid cancer had higher levels of serum malondialdehyde (MDA), another biomarker of lipid peroxidation, compared to the healthy control group (M Gerić, 2016; M. Akinci, 2008). We did not observe evidence of the association between 8-OHdG, a biomarker of DNA damage, and the risk of thyroid cancer. A similar result was also reported in another study, in which no significant difference existed in terms of urinary 8-OHdG between the papillary thyroid carcinoma and the controls (Ece et al., 2013). In contrast, Tabur et al. (2015) found a significantly higher level of serum 8-OHdG in preoperative thyroid papillary cancer patients compared with both the postoperative group and controls. One possible explanation for the discrepancy is that 8-OHdG measured in urine and serum may reflect different status of individual's DNA damage.

To our knowledge, this is the first epidemiological study exploring the potential mediating role of oxidative stress in the associations between phenol exposures and thyroid cancer. The results of our mediation analysis showed that urinary 8-isoPGF$_{2\alpha}$ mediated part of the associations between TCS, BPA, BPS exposures and increased risk of thyroid cancer, suggesting that lipid peroxidation as an intermediate mechanism may participate in the phenol-induced thyroid oncogenesis. In support of our results, rats orally exposed to BPA for 35 days induced overproduction of reactive oxygen species and significant decreases of superoxide dismutase activity and glutathione levels, as well as significant increases of myeloperoxidase activity and MDA levels, and eventually leading to increased DNA damage in the thyroid gland and thyroid hormonal disruption (Mohammed et al., 2020).

Our study has several limitations. First, we synchronously evaluated the exposure, mediator and outcome, and thus the causal relationships of phenols exposure with the risk of thyroid cancer, as well as the mediating effects of oxidative stress on these associations, were difficult to elucidate. Second, our subjects were recruited from hospital, and the selection bias occurs inevitably. Extrapolations of our findings to other populations should be cautious. In addition, our sample size was not large enough, which may result in imprecise estimations. Third, a single measurement of urinary biomarkers may not be representative of long-term phenol exposure and oxidative stress status due to their short biological half-lives in human body. Several studies have demonstrated that concentrations of urinary phenols and oxidative stress biomarkers exhibited high within-day variability (Morgan et al., 2018; Pollack et al., 2016; Wang et al., 2019). Misclassification of measurements in phenol exposures and oxidative stress biomarkers may have biased the observed results. Finally, humans are exposed to numerous environmental chemicals simultaneously, other substances, such as phthalates and persistent organic pollutants, have been reported to be associated with thyroid cancer that were not considered in this study (Freeman et al., 2011; Lerro et al., 2015; Liu et al., 2020). Moreover, some important risk factors for thyroid cancer, such as iodine intake and thy-

roid stimulating hormone levels, were not measured. So, the findings of the study may reflect a mixed effect, rather than the effects of phenols alone, which may lead to false positive conclusions. Future studies linking environmental exposure and disease outcome should place more emphasis on exposomic approach, as well as other metabolic processes that may mediate the toxicological pathway (Sun et al., 2021).

4.　　Conclusion

In this study, we found that urinary TCS, BPA and BPS were associated with increased risk of thyroid cancer, and urinary 8-isoPGF$_{2\alpha}$ played a mediating role in these associations. Our findings advance the understanding of phenol exposure associated with thyroid cancer and further uncover that lipid peroxidation may be a biological mechanism through which phenol exposure induces tumorigenesis of thyroid. However, future studies with larger-scaled design and more precise assessment of exposures and mediators are encouraged to confirm our findings.

Acknowledgments

Appendix A Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jes.2022.01.009.

REFERENCES

An, J., He, H., Yao, W., Shang, Y., Jiang, Y., Yu, Z., 2020. PI3K/Akt/FoxO pathway mediates glycolytic metabolism in HepG2 cells exposed to triclosan (TCS). Environ. Int. 136, 105428.

Axelstad, M., Boberg, J., Vinggaard, A.M., Christiansen, S., Hass, U., 2013. Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and in directly exposed offspring. Food Chem. Toxicol. 59, 534–540.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113, 192–200.

Casas, M., Valvi, D., Luque, N., Ballesteros-Gomez, A., Carsin, A.E., Fernandez, M.F., et al., 2013. Dietary and sociodemographic determinants of bisphenol A urine concentrations in pregnant women and children. Environ. Int. 56, 10–18.

Chen, D., Kannan, K., Tan, H., Zheng, Z., Feng, Y.L., Wu, Y., et al., 2016. Bisphenol analogues other Than BPA: environmental occurrence, human exposure, and toxicity-a review. Environ. Sci. Technol. 50, 5438–5453.

Cui, F.P., Yang, P., Liu, C, Chen P,, P, Deng L,, Y, Miao, Y, et al., 2021. Urinary bisphenol A and its alternatives among pregnant

women: predictors and risk assessment. Sci. Total Environ. 784, 147184.

Silva, M.M., M, M, Goncalves, C.F. L., Miranda-Alves, L., Fortunato, R.S., Carvalho, D.P., Ferreira, A.C.F., 2019. Inhibition of Type 1 Iodothyronine Deiodinase by Bisphenol A. Horm. Metab. Res. 51, 671–677.

Ece, H., Mehmet, E., Cigir, B.A., Yavuz, D., Muammer, K., Cumhur, G., et al., 2013. Serum 8-OHdG and HIF-1α levels: do they affect the development of malignancy in patients with hypoactive thyroid nodules? Contemp Oncol (Pozn) 17, 51–57.

Farasani, A., Darbre, P.D., 2020. Long-term exposure to triclosan increases migration and invasion of human breast epithelial cells in vitro. J. Appl. Toxicol..

Ferguson, K.K., Lan, Z., Yu, Y., Mukherjee, B., McElrath, T.F., Meeker, J.D., 2019. Urinary concentrations of phenols in association with biomarkers of oxidative stress in pregnancy: Assessment of effects independent of phthalates. Environ. Int. 131, 104903.

Fernandez, M.O., Bourguignon, N.S., Arocena, P., Rosa, M., Libertun, C., Lux-Lantos, V., 2018. Neonatal exposure to bisphenol A alters the hypothalamic-pituitary-thyroid axis in female rats. Toxicol. Lett. 285, 81–86.

Freeman, L.E., Rusiecki, J.A., Hoppin, J.A., Lubin, J.H., Koutros, S., Andreotti, G., et al., 2011. Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994-2007). Environ. Health Perspect. 119, 1253–1259.

Gomes, M.F., Paula, V.C.S., Martins, L.R.R., L, R, Garcia, J.R.E., J, R, Yamamoto, F.Y., Freitas, A.M., 2020. Sublethal effects of triclosan and triclocarban at environmental concentrations in silver catfish (Rhamdia quelen) embryos. Chemosphere 263, 127985.

Gorini, F., Bustaffa, E., Coi, A., Iervasi, G., Bianchi, F., 2020. Bisphenols as Environmental Triggers of Thyroid Dysfunction: Clues and Evidence. Int. J. Environ. Res. Public Health 17.

Hinther, A., Bromba, C.M., Wulff, J.E., Helbing, C.C., 2011. Effects of triclocarban, triclosan, and methyl triclosan on thyroid hormone action and stress in frog and mammalian culture systems. Environ. Sci. Technol. 45, 5395–5402.

Hornung, R.W., Reed, L.D., 1990. Estimation of average concentration in the presence of nondetectable values. Appl. Occup. Environ. Hyg. 5, 46–51.

Hu, J., Zhao, H., Braun, J.M., Zheng, T., Zhang, B., Xia, W., et al., 2019. Associations of trimester-specific exposure to bisphenols with size at birth: a Chinese prenatal cohort Study. Environ. Health Perspect. 127, 107001.

Huang, M, Liu, S, Fu, L, Jiang, X, Yang, M, 2020a. Bisphenol A and its analogues bisphenol S, bisphenol F and bisphenol AF induce oxidative stress and biomacromolecular damage in human granulosa KGN cells. Chemosphere 253.

Huang, Y, Li, X, Zhang, W, Su, W, Zhou, A, Xu, S, et al., 2020b. Aluminum exposure and gestational diabetes mellitus: associations and potential mediation by n-6 Polyunsaturated fatty acids. Environ. Sci. Technol. 54, 5031–5040.

Il'yasova, D., Scarbrough, P., Spasojevic, I., 2012. Urinary biomarkers of oxidative status. Clin. Chim. Acta 413, 1446–1453.

Jiang, W., Cao, L., Wang, F., Ge, H., Wu, P.C., Li, X.W., et al., 2016. Accelerated reduction of serum thyroxine and hippocampal histone acetylation links to exacerbation of spatial memory impairment in aged CD-1 mice pubertally exposed to bisphenol-a. Age (Dordr) 38, 405–418.

Klaunig, J.E., 2018. Oxidative stress and cancer. Curr. Pharm. Des. 24, 4771–4778.

Kwon, J.A., Shin, B., Kim, B., 2020. Urinary bisphenol A and thyroid function by BMI in the Korean National environmental health survey (KoNEHS) 2012-2014. Chemosphere 240, 124918.

Lee, S., Kim, C., Shin, H., Kho, Y., Choi, K., 2019. Comparison of

thyroid hormone disruption potentials by bisphenols A, S, F, and Z in embryo-larval zebrafish. Chemosphere 221, 115–123.

Lerro, C.C., Freeman, B.L.E., L, E, DellaValle, C.T., Andreotti, G., Hofmann, J.N., Koutros, S., et al., 2021. Pesticide exposure and incident thyroid cancer among male pesticide applicators in agricultural health study. Environ. Int. 146, 106187.

Lerro, C.C., Koutros, S., Andreotti, G., Friesen, M.C., Alavanja, M.C., Blair, A., et al., 2015. Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. Occup. Environ. Med. 72, 736–744.

Li, L., Li, H., Zhang, J., Gao, X., Jin, H., Liu, R., et al., 2021. Bisphenol A at a human exposed level can promote epithelial-mesenchymal transition in papillary thyroid carcinoma harbouring BRAF(V600E) mutation. J. Cell. Mol. Med. 25, 1739–1749.

Li, M., Maso, L.D., Vaccarella, S., 2020. Global trends in thyroid cancer incidence and the impact of overdiagnosis. Lancet Diabetes Endo 8, 468–470.

Liu, C., Deng, Y.L., Zheng, T.Z., Yang, P., Jiang, X.Q., Liu, E.N., et al., 2020. Urinary biomarkers of phthalates exposure and risks of thyroid cancer and benign nodule. J. Hazard. Mater. 383.

Lv, Y., Rui, C., Dai, Y., Pang, Q., Li, Y., Fan, R., et al., 2016. Exposure of children to BPA through dust and the association of urinary BPA and triclosan with oxidative stress in Guangzhou. China. Environ. Sci .Process. Impacts 18, 1492–1499.

Gerić, M., A, M.D., Gluščić, V., Janušić, R., Šarčević, B., Gj-Vrhovac, V., 2016. Cytogenetic status and oxidative stress parameters in patients with thyroid diseases. Mutat. RES-GEN. TOX. EN. 810, 22–29.

Akinci, M.F.K., F, K, Cetin, B., Sepici, A., Altan, N., Aslan, S., Cetin, A., 2008. Oxidant/antioxidant balance in patients with thyroid cancer. Acta Cirurgica Brasileira 23, 551–554.

Marotta, V., Russo, G., Gambardella, C., Grasso, M., Sala, D.L., Chiofalo, M.G., M, G, et al., 2019. Human exposure to bisphenol AF and diethylhexylphthalate increases susceptibility to develop differentiated thyroid cancer in patients with thyroid nodules. Chemosphere 218, 885–894.

Miranda-Filho, A., Lortet-Tieulent, J., Bray, F., Cao, B., Franceschi, S., Vaccarella, S., et al., 2021. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. LANCET DIABETES ENDO 9, 225–234.

Mohammed, E.T., Hashem, K.S., Ahmed, A.E., Aly, M.T., Aleya, L., Abdel-Daim, M.M., 2020. Ginger extract ameliorates bisphenol A (BPA)-induced disruption in thyroid hormones synthesis and metabolism: Involvement of Nrf-2/HO-1 pathway. Sci. Total Environ. 703, 134664.

Morgan, M.K., Nash, M., Barr, D.B., Starr, J.M., Clifton, S.M., Sobus, J.R., J, R, 2018. Distribution, variability, and predictors of urinary bisphenol A levels in 50 North Carolina adults over a six-week monitoring period. Environ. Int. 112, 85–99.

Mukherjee, U., Samanta, A., Biswas, S., Das, S., Ghosh, S., Mandal, D.K., et al., 2020. Bisphenol A-induced oxidative stress, hepatotoxicity and altered estrogen receptor expression in Labeo bata: impact on metabolic homeostasis and inflammatory response. Ecotoxicol. Environ. Saf. 202, 110944.

Paul, K.B., Hedge, J.M., Bansal, R., Zoeller, R.T., Peter, R., DeVito, M.J., et al., 2012. Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology 300, 31–45.

Petrakis, D., Vassilopoulou, L., Mamoulakis, C., Psycharakis, C., Anifantaki, A., Sifakis, S., et al., 2017. Endocrine disruptors leading to obesity and related diseases. Int. J. Environ. Res. Public Health 14, 1–18.

Pollack, A.Z., Perkins, N.J., Sjaarda, L., Mumford, S.L., Kannan, K., Philippat, C., et al., 2016. Variability and exposure classification of urinary phenol and paraben metabolite concentrations in reproductive-aged women. Environ. Res. 151, 513–520.

Qiu, W., Yang, M., Liu, J., Xu, H., Luo, S., Wong, M., et al., 2019. Bisphenol S-induced chronic inflammatory stress in liver via peroxisome proliferator-activated receptor gamma using fish in vivo and in vitro models. Environ. Pollut. 246, 963–971.

SAS Institute Inc, 2020. SAS/STAT® 15.2 User's Guide. SAS Institute Inc, Cary, NC.

Sauer, P., Svecova, H., Grabicova, K., Gonul Aydin, F., Mackulak, T., Kodes, V., et al., 2021. Bisphenols emerging in Norwegian and Czech aquatic environments show transthyretin binding potency and other less-studied endocrine-disrupting activities. Sci. Total Environ. 751, 141801.

Silva, M.M.D., Xavier, L.L.F., Goncalves, C.F.L., Santos-Silva, A.P., Paiva-Melo, F.D., Freitas, M.L., et al., 2018. Bisphenol A increases hydrogen peroxide generation by thyrocytes both in vivo and in vitro. Endocr Connect 7, 1196–1207.

Smith, K.W., Braun, J.M., Williams, P.L., Ehrlich, S., Correia, K.F., Calafat, A.M., et al., 2012. Predictors and variability of urinary paraben concentrations in men and women, including before and during pregnancy. Environ. Health Perspect. 120, 1538–1543.

Sun, J., Fang, R., Wang, H., Xu, D.X., Yang, J., Huang, X., et al., 2021. A review of environmental metabolism disrupting chemicals and effect biomarkers associating disease risks: Where exposomics meets metabolomics. Environ. Int. 158, 106941.

Tabur, S., Aksoy, S.N., Korkmaz, H., Ozkaya, M., Aksoy, N., Akarsu, E., 2015. Investigation of the role of 8-OHdG and oxidative stress in papillary thyroid carcinoma. Tumour Biol 36, 2667–2674.

Ullah, A., Pirzada, M., Afsar, T., Razak, S., Almajwal, A., Jahan, S., 2019. Effect of bisphenol F, an analog of bisphenol A, on the reproductive functions of male rats. Environ. Health Prev. Med. 24, 41.

Valeri, L., Vanderweele, T.J., 2013. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol. Methods 18, 137–150.

VanderWeele, L.V.T.J., 2013. Supplemental material for mediation analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol. Methods 18, 137–150.

Wang, D., Feng, J.F., Zeng, P., Yang, Y.H., Luo, J., Yang, Y.W., 2011. Total oxidant/antioxidant status in sera of patients with thyroid cancers. Endocr. Relat. Cancer 18, 773–782.

Wang, J., Mei, H., Zhou, A.F., Huang, L.L., Cao, Z.Q., Hong, A.B., et al., 2021. The associations of birth outcome differences in twins with prenatal exposure to bisphenol A and its alternatives. Environ. Res. 200, 111459.

Wang, J., Yu, F., Shang, Y., Ping, Z., Liu, L., 2020. Thyroid cancer: incidence and mortality trends in China, 2005-2015. Endocrine 68, 163–173.

Wang, Y.X., You, L., Zeng, Q., Sun, Y., Huang, Y.H., Wang, C., et al., 2015. Phthalate exposure and human semen quality: Results from an infertility clinic in China. Environ. Res. 142, 1–9.

Wang, Y.X., Liu, C., Shen, Y., Wang, Q., Pan, A., Yang, P., et al., 2019. Urinary levels of bisphenol A, F and S and markers of oxidative stress among healthy adult men: Variability and association analysis. Environ. Int. 123, 301–309.

Wu, Y., Beland, F.A., Fang, J.L., 2016. Effect of triclosan, triclocarban, 2,2′,4,4′-tetrabromodiphenyl ether, and bisphenol A on the iodide uptake, thyroid peroxidase activity, and expression of genes involved in thyroid hormone synthesis. Toxicol. In Vitro 32, 310–319.

Young, O., Crotty, T., O'Connell, R., O'Sullivan, J., Curran, A.J., 2010. Levels of oxidative damage and lipid peroxidation in thyroid neoplasia. Head Neck 32, 750–756.

Zhang, T., Xue, J., Gao, C.Z., Qiu, R.L., Li, Y.X., Li, X., et al., 2016. Urinary concentrations of bisphenols and their association with biomarkers of oxidative stress in people living near E-waste recycling facilities in China. Environ. Sci. Technol. 50, 4045–4053.

Zhang, Y., Wei, F., Zhang, J., Hao, L., Jiang, J., Dang, L., et al., 2017. Bisphenol A and estrogen induce proliferation of human thyroid tumor cells via an estrogen-receptor-dependent pathway. Arch. Biochem. Biophys. 633, 29–39.

Zhang, Y.F., Ren, X.M., Li, Y.Y., Yao, X.F., Li, C.H., Qin, Z.F., et al., 2018. Bisphenol A alternatives bisphenol S and bisphenol F interfere with thyroid hormone signaling pathway in vitro and in vivo. Environ. Pollut. 237, 1072–1079.

Zhou, Z., Zhang, J., Jiang, F., Xie, Y., Zhang, X., Jiang, L., 2017. Higher urinary bisphenol A concentration and excessive iodine intake are associated with nodular goiter and papillary thyroid carcinoma. Biosci. Rep. 37.