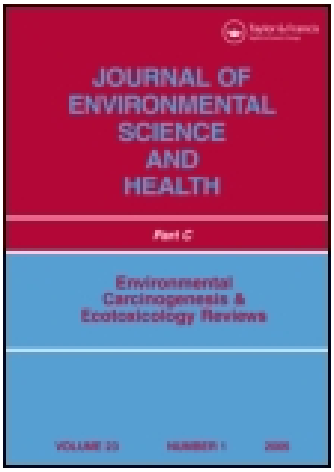

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Thyroid Disrupting Chemicals in Plastic Additives and Thyroid Health

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Thyroid Disrupting Chemicals in Plastic Additives and Thyroid Health

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The globally escalating thyroid nodule incidence rates may be only partially ascribed to better diagnostics, allowing for the assessment of environmental risk factors on thyroid disease. Endocrine disruptors or thyroid-disrupting chemicals (TDC) like bisphenol A, phthalates, and polybrominated diphenyl ethers are widely used as plastic additives in consumer products. This comprehensive review studied the magnitude and uncertainty of TDC exposures and their effects on thyroid hormones for sensitive subpopulation groups like pregnant women, infants, and children. Our findings qualitatively suggest the mixed, significant ($\alpha = 0.05$) TDC associations with natural thyroid hormones (positive or negative sign). Future studies should undertake systematic meta-analyses to elucidate pooled TDC effect estimates on thyroid health indicators and outcomes.

Keywords: bisphenol A; phthalates; plastic additives; polybrominated diphenyl ethers; thyroid disruption; thyroid-disrupting chemicals (TDC); thyroid hormones; total triiodothyronine (T3); free triiodothyronine (FT3); thyroxine (T4); free thyroxine (FT4); thyroid-stimulating hormone (TSH)

1. INTRODUCTION

Noncommunicable diseases, such as cancer, diabetes, cardiovascular, and chronic respiratory diseases, are predicted to cost more than US $30 trillion, representing 48% of global GDP in 2010, over the next 20 years [1]. Such comprehensive disease predictive models often assume a constant number of annual new incidence cases for a specific outcome, but often this is not

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the case; an illustrating example is thyroid cancer, which appears as the outcome with the highest change in annual excess number of new cases in the developed world [1]. The widespread availability of ultrasonographs (US), price reduction, and subsequently increased frequency of use worldwide is believed to be a major factor behind the skyrocketed incidence rates of thyroid anomalies, including cancer. As an illustrating example, thyroid nodule prevalence has risen in the past 2 decades to nearly 4%–7% and 50%–60% of the United States upon simple palpation and autopsy, respectively [2]. An illustrating example of increased thyroid abnormalities in the European Union is the Cypriot population that is currently experiencing skyrocketed world age standardized incidence rates of thyroid cancer, reaching from 8.4 and 1.8 per 100,000 in 1999 up to 17 and 4 cases per 100,000 by 2009, in women and men, respectively, (Cypriot Ministry of Health, 2011, Dr. Pavlou, personal communication). Despite the relative increase in diagnosis of malignant thyroid nodules < 1 cm, surprising results in the cohort of [3] illustrated an increase in large tumors (> 4 cm), but not in the frequency of detected tumors in the size range of 2–4 cm [3]. Similarly, doubling of the incidence rates for thyroid cancers of > 2 cm and also for > 4 cm and > 6 cm was observed from 1983–2006 [4]. It is hard to assign the increased incidences of large thyroid nodules (> 4 cm) to simply better diagnostic tools, thus eluding us to suspect other disease risk-based etiologic agents that could have influenced the burden of thyroid disease, such as environmental risk factors.

Better exposure science via comprehensive analysis of environmental exposures is needed for improving our understanding on the development of thyroid anomalies, in light of recent findings attributing the highest proportion of the observed burden of disease to environmental rather than to genetic factors [5]. Endocrine-disrupting chemicals, or better say, thyroid-disrupting chemicals (TDC), are synthetic chemicals in everyday consumer products mimicking or antagonizing natural thyroid hormone processes. Plastic additives or plasticizers are chemicals that enhance flexibility and/or processing of plastic materials used in widely used consumer products. Bisphenol A (BPA), phthalates, and polybrominated diphenyl ethers (PBDE) are illustrating examples of TDC widely used as plastic additives in everyday consumer products worldwide [6–11]. Evidence is piling up for TDC effects on thyroid gland perturbations alterations in thyroid hormones (TH), and associated adverse effects on fetus/infant/child development [12–15].

Recent literature suggested subclinical alterations in TH circulating levels due to presence of TDC affecting both the endocrine and the central nervous system. Upon human consumption, food- and water-containing TDC after contact with plastic packaging materials enter the circulating system through the gastrointestinal tract. The central nervous system works closely with the thyroid gland in regulating TH production, secretion, and elimination via the feedback loop activation of the hypothalamus pituitary thyroid axis (HPT) [16].

The TDC blood circulation and/or local circulation within tissues such as hepatocytes could adversely impact TH production and metabolism in the thyroid gland impacting other organs, such as brain, primarily in critical developmental stages. It is anticipated that TDC in circulating blood would form complexes with protein-TH that will eventually reach brain and bind to TH receptors. TDC may also be associated with the prevalence of subclinical thyroid condition, also known as subclinical thyroid disease (SCTD). SCTD is a condition where malfunctioning of the HPT axis is typically associated with the occurrence of abnormal TSH levels in serum while having free thyroxine (FT4) and free triiodothyronine (FT3) levels remaining within reference range. SCTD is characterized either by undetectable to low serum TSH in case of subclinical hyperthyroidism or higher levels in case of subclinical hypothyroidism [17–20]. In addition, timing of thyroid hormone action [21,22] and stage of brain development [23–26] could determine the extent of disruption of thyroid function due to environmental chemical exposures. Moreover, TDC exposures directly interfering with thyroid hormone receptors may not yield immediate changes in circulating TH levels despite the pronounced effects on HPT axis [27]. Although fluctuations in serum TH concentrations were associated with qualitative and/or quantitative changes in animal brain development processes, no such clinical indicators of diagnostic value are available for measuring TDC effects on thyroid health in population studies [28]. Thus, it is of great interest to improve science toward support for decision and policymaking on the subclinical TDC population exposure effects on thyroid health.

This comprehensive review gathered human studies available to date about the magnitude and uncertainty associated with exposures to specific TDC, such as BPA, phthalates, PBDE, and their effects on natural as measured TH for various sensitive subpopulation groups. Primary focus was placed upon methodological aspects and findings of human exposure science studies dealing with TDC effects on thyroid health as expressed via measurements of total triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4), free thyroxine (FT4), and thyroid-stimulating hormone (TSH).

2. LITERATURE COLLECTION AND DATA PRESENTATION

A literature search from 1980–2011 was conducted using MEDLINE, Scopus (Elsevier), and ISI Web of Knowledge databases adapting the following inclusive criteria: (1) only human exposure studies; (2) both environmental and occupational exposures to humans from plastic additives; (3) studies including bisphenol A, phthalates, and/or PBDEs analyses in human biofluids; (4) studies including data on one or more of the selected five natural thyroid hormones (T3, FT3, T4, FT4, TSH); and (5) presentation of quantitative multivariate regression analyses, between the exogenous TDC and the natural

thyroid hormones in human biofluids. The keywords used for database searching were "endocrine disruptor* AND thyroid AND biomarker*", "endocrine disruptor* AND thyroid hormone*", "bisphenol* AND thyroid", "phthalate* AND thyroid", "PBDE* AND thyroid", and a combination of these keywords with individual thyroid hormones. Peer-reviewed manuscripts in English were considered, while conference abstracts and information on the World Wide Web were excluded. In addition, the cited bibliography in each of the journal manuscripts of interest was thoroughly screened to obtain back referenced material relating to the topic of this review. This review provides a thorough and up to date compilation of biomonitoring studies available on thyroid health biomarkers (thyroid hormones) in relation to endocrine-, and in particular, thyroid-disrupting chemicals found in plastics.

In human matrices, four relevant studies were identified that measured BPA [29,41,42,49], five studies on phthalates metabolites [29,50,60,74,79], and seventeen studies on PBDEs and their metabolites [42,114,120,126, 127,135,136,139,144,153,155,161,167,170–172,186] while reporting with their respective associations with serum thyroid hormones (Tables 1–3). Studies under each TDC were classified into five broad subject categories: general population, occupationally-exposed, pregnant women and infants, children and adolescents, and adults.

Data was abstracted from studies listed in Tables 1, 2, and 3 and were expressed in the form of mean and standard deviation for both plastic additive analyte of interest and the five serum thyroid hormones. Variations in descriptive statistics, measurement units, and differences in human matrices used for analyses under each study were presented as footnotes in Table 1, which is the same for the rest of the tables. Direction (sign) of associations between the TDC and a specific serum TH measured in each study was expressed with the following arrows: (a) ↑ (positive), (b) ↓ (negative), (c) ↔ (no distinct association), and (d) – (association not measured or presented). Associations were inferred either from the text or from the correlation and/or regression coefficients presented in each study. Statistical significance of each association was also represented with increasing number of asterisks to represent $p \leq 0.10$, 0.05, 0.01, and 0.001, respectively (Table 1–3).

3. PLASTIC ADDITIVES ALTER THYROID HORMONES STATUS: HUMAN EXPOSURE STUDIES

3.1. Bisphenol-A (BPA)

It is important to note that the acronym BPA used throughout this article refers to total BPA in biological matrices that may also include conjugated BPA metabolites, primarily bisphenol A-glucuronide, unless otherwise specified. It

Table 1: Magnitude and Variability of Bisphenol A in Human Biologic Fluids and Associated Thyroid Hormone Concentrations; Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients and Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study.

		Bisphenol A	Serum Thyroid Hormones Levels and Relations with TDC										
		(μg g^{-1} C)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]		
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
Bisphenol A													
1	[29] Meeker and Ferguson, 2011 (USA)												
	≥ 20 y NHANES study adults [1405, ≥ 20 y, stratified BMI]	1.92[a]	111[a]	↓	3.2[a]	↓	760[a]	↓**	0.8[a]	↑	1.6[a]	↓	
	12–19 y NHANES study adolescents [355, 12–19 y, stratified BMI]	1.67[a]	126[a]	↑	3.6[a]	↓	730[a]	↓	0.8[a]	↑	1.4[a]	↑	
2	[41] Sugiura-Ogasawara et al., 2005 (Japan)												
	Patients (≥ 3 miscarriages) [45, 31.6 ± 4.4, 20.9 ± 2.7]	BPA 2.59 ± 5.23[b1]	NM	–	NM	–	NM	–	NP	↔	NP	↔	
	Control (healthy) [32, 32.0 ± 4.8, 20.81 ± 2.25]	BPA 0.77 ± 0.38[b1]	NM	–	NM	–	NM	–	NP	↔	NP	↔	
3	[42] Wan et al., 2010 (South Korea)												
	Pregnant women [26, 31 ± 4.7, 21.6 ± 4.2]	BPA 0.7 ± 0.1[b1]	NM	–	NM	–	9.7 ± 1.8	–	NM	–	NM	–	

(*Continued on next page*)

Table 1: Magnitude and Variability of Bisphenol A in Human Biologic Fluids and Associated Thyroid Hormone Concentrations; Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients and Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study (*Continued*).

		Bisphenol A	**Serum Thyroid Hormones Levels and Relations with TDC**										
		(μg g^{-1} C)[b]	**T3 (ng dL^{-1})[c]**		**FT3 (pg mL^{-1})[d]**		**T4 (μg dL^{-1})[e]**		**FT4 (ng dL^{-1})[f]**		**TSH (μIU mL^{-1})[g]**		
#	**Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]**	**Mean ± SD**	**Mean ± SD**	**Trend**	**Mean ± SD**	**Trend**	**Mean ± SD**	**Trend**	**Mean ± SD**	**Trend**	**Mean ± SD**	**Trend**	**OR**
	Fetus [28, NM, 3.11 ± 0.46]	BPA < 0.6[a, b1]	NM	–	NM	–	8.5 ± 1.7	–	NM	–	NM	–	
4	[49] Meeker et al., 2010 (USA) Fertility study men [167, 37 ± 5.3, 27 ± 4.6]	BPA 1.3[a, b2]	9.4	↑	NM	–	NM	–	1.14	↑	1.43	↑	

NM–not mentioned; NP – mentioned but data not presented.
*, **, ***, **** represent $p \leq 0.10, 0.05, 0.01$, and 0.001, respectively.
[a]Median value as the descriptive statistic; [a1]geometric mean (GM) as the descriptive statistic; [a$]inferred from graphs.
[b]Analyte levels expressed in a different unit and/or different matrix other than standard representation of μg g^{-1}creatinine in urine.
[b1]ng mL^{-1} serum/lipid; [b2]ng mL^{-1} urine; [b3]ng g^{-1} serum/lipid; [b4]ng g^{-1} cord blood/lipid; [b5]ng g^{-1} house dust.
[c]T3 analysis in a different matrix and/or reporting in a different unit other than the standard representation of ng dL^{-1} serum/lipid.
[c1]nmol L^{-1} serum/lipid; [c2]nmol L^{-1} plasma/lipid; [c3]ng dL^{-1} cord blood/lipid; [c4]nmol L^{-1} cord serum/lipid.
[d]FT3 analysis in a different matrix and/or reporting in a different unit other than the standard representation of pg mL^{-1} serum/lipid.
[d1]pmol L^{-1} plasma/lipid; [d2]pg mL^{-1} cord blood/lipid.
[e]T4 analysis in a different matrix and/or reporting in a different unit other than the standard representation of μg dL^{-1} serum/lipid.
[e1]IU L^{-1} serum/lipid; [e2]nmol L^{-1} plasma/lipid; [e3]μg dL^{-1} cord blood/lipid; [e4]mcg dL^{-1}; [e4]nmol L^{-1} cord serum/lipid.
[f]FT4 analysis in a different matrix and/or reporting in a different unit other than the standard representation of ng dL^{-1} serum/lipid.
[f1]pmol L^{-1} serum/lipid; [f2]pmol L^{-1} plasma/lipid; [f3]ng mL^{-1} serum/lipid; [f4]ng dL^{-1} cord blood/lipid; [f5]pmol L^{-1} cord serum/lipid.
[g]TSH analysis in a different matrix and/or reporting in a different unit other than the standard representation of μIU mL^{-1} serum/lipid.
[g1]IU L^{-1} serum/lipid; [g2]μIU mL^{-1} cord blood/lipid; [g3]μIUg mL^{-1} cord blood/lipid; [g4]GM ± GD μIU mL^{-1} serum/lipid; [g5]nmol L^{-1} cord serum/lipid; [g6]mcIU mL^{-1} cord blood/lipid; [g7]mIU mL^{-1} serum/lipid.

Table 2: Magnitude and Variability of Phthalates in Human Biologic Fluids and Associated Thyroid Hormone Concentrations. ¥Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients And Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study.

		Phthalates Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites										
		(μg g^{-1} C.)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]		
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
Phthalates													
1	[50] Huang et al., 2007 (Taiwan)												
	Pregnant women [76, 33.6 ± 3.3, 20.9 ± 2.5]	MEP 68.0[a,b], 27.7[a,b2]	132.0[a]	↓	NM	–	8.85[a]	↓	0.93[a]	↑	1.1[a]	↓	
		MBP 195.0[a,b], 81.8[a,b2]		↓**		–		↓**		↓**		↓	
		MBzP 3.7[a,b], 0.9[a,b2]		↓		–		↑		↑		↓	
		MEHP 60.8[a,b], 20.6[a,b2]		↓		–		↑		↑		↓	
		MMP 10.8[a,b],4.3[a,b2]		↓		–		↓		↓		↓	
2	[60] Boas et al., 2010 (Denmark)												
	Boys-School Children [503, 6.9 ± 1.4, 15.7 ± 1.6]	MEP 31.0[a]	NP	↓	NP	↓	NP	↑	NP	↑	NP	↑	
		MBP 191.0[a]		↓		↓***		↓		↓		↓	
		MBzP 26.0[a]		↓		↓		↓		↓		↔	
		MEHP 6.8[a]		↓		↓		↑		↑		↓	
		MEHHP 52.0[a]		↑		↓		↑		↑		↓	
		MEOHP 26.0[a]		↔		↓		↑		↑		↔	
		MECCP 43.0[a]		↓		↓		↑		↑		↓	
		MOP 0.0[a]		–		–		–		–		–	
		MiNP 1.0[a]		–		–		–		–		–	
		MHiNP 8.4[a]		↓		↓		↓		↑		↑	
		MOiNP 4.1[a]		↓		↓		↓		↑		↑	
		MCiOP 10.0[a]		↓		↓***		↓		↓		↑	
		∑DEHP-metabolites		↔		↓		↑		↑		↓	
		Phthalate Score		↔		↑		↑		↔		↔	

(*Continued on next page*)

Table 2: Magnitude and Variability of Phthalates in Human Biologic Fluids and Associated Thyroid Hormone Concentrations. ¥Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients And Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study *(Continued)*.

		Phthalates Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites									
		(μg g^{-1} C.)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]	
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
	Girls-School Children	MEP 36.0[a]	NP	$\downarrow^{****}$	NP	$\downarrow^{**}$	NP	$\downarrow^{**}$	NP	↓	NP	↑	
	[503, 6.9 ± 1.4, 15.7 ± 1.6]	MBP 227.0[a]		$\downarrow^{***}$		↓		↓		↑		↑	
		MBzP 20.0[a]		$\downarrow^{**}$		↓		↓		↓		↓	
		MEHP 6.7[a]		$\downarrow^{**}$		↓		↓		↓		↑	
		MEHHP 52.0[a]		$\downarrow^{**}$		$\downarrow^{**}$		↓		↓		↑	
		MEOHP 28.0[a]		$\downarrow^{**}$		$\downarrow^{**}$		↓		↓		↑	
		MECCP 49.0[a]		$\downarrow^{**}$		$\downarrow^{**}$		↓		↓		↔	
		MOP 0.0[a]		–		–		–		–		–	
		MiNP 1.1[a]		–		–		–		–		–	
		MHiNP 7.4[a]		↓		↔		↑		↑		↓	
		MOiNP 3.9[a]		↓		↓		↑		↔		↓	
		MCiOP 12.0[a]		↓		↓		↓		↑		$\downarrow^{**}$	
		∑DEHP-metabolites		$\downarrow^{**}$		$\downarrow^{**}$		↓		↓		↑	
		Phthalate Score		$\downarrow^{*}$		$\downarrow^{**}$		$\downarrow^{**}$		↓		↔	
3	[29] Meeker and Ferguson, 2011 (USA)												
	≥ 20 y NHANES study adults	MEHP 2.29[a]	111.0[a]	↓	3.2[a]	↓	760.0[a]	$\downarrow^{***}$	0.8[a]	↓	1.6[a]	↑	
	[1405, ≥ 20 y, stratified BMI]	MEHHP 18.23[a]		$\downarrow^{**}$		↓		$\downarrow^{**}$		↓		$\uparrow^{***}$	
		MEOHP 9.76[a]		$\downarrow^{**}$		↓		$\downarrow^{**}$		↓		$\uparrow^{***}$	
		MECCP 26.4[a]		↓		↑		$\downarrow^{**}$		↓		$\uparrow^{**}$	
		MiBP 6.67[a]		↑		↓		↑		↑		↑	
		MnBP 17.1[a]		↑		↓		↑		↑		↓	
		MCPP 2.26[a]		↓		$\downarrow^{***}$		↓		↑		↑	

	12–19 yrs NHANES study adolescents [355, 12–19 yrs, stratified BMI]	MEHP 2.00[a]	126.0[a]	↑****	3.6[a]	↑**	730.0[a]	↑	0.8[a]	↓	1.4[a]	↓
		MEHHP 20.33[a]		↑***		↑		↑		↑		↑
		MEOHP 11.44[a]		↑***		↑		↑		↓		↑
		MECCP 27.8[a]		↑***		↑		↑		↑		↑
		MiBP 8.24[a]		↑		↑		↓		↓		↓
		MnBP 21.93[a]		↑		↑		↓		↓		↓
		MCPP 2.93[a]		↑		↑		↓***		↓**		↓
4	[79] Janjua et al., 2007 (Denmark)											
	Young men-Control Week [26, 26 ± 4, 24 ± 2]											
	0h	MEP 6 ± 1[b1]	1.6 ± 0.3[c1]	↔	NM	–	72 ± 13[e1]	↔	12.3 ± 1.3[f1]	↔	1.51 ± 0.31[g1]	↔
	1h	MEP 28 ± 5[b1]	1.6 ± 0.3[c1]	↔		–	72 ± 13[e1]	↔	12.1 ± 1.2[f1]	↔	1.27 ± 0.57[g1]	↔
	2h	MEP 13 ± 1[b1]	1.7 ± 0.3[c1]	↔		–	70 ± 11[e1]	↔	12.2 ± 1.2[f1]	↔	1.24 ± 0.54[g1]	↔
	3h	MEP 12 ± 2[b1]	1.6 ± 0.2[c1]	↔		–	72 ± 11[e1]	↔	12.3 ± 1.6[f1]	↔	1.22 ± 0.51[g1]	↔
	4h	MEP 10 ± 2[b1]	1.6 ± 0.3[c1]	↔		–	71 ± 11[e1]	↔	12.1 ± 1.0[f1]	↔	1.41 ± 0.76[g1]	↔
	24h	MEP 6 ± 1[b1]	1.7 ± 0.2[c1]	↔		–	77 ± 13[e1]	↔	12.8 ± 1.4[f1]	↔	1.55 ± 0.68[g1]	↔
	96h	MEP 6 ± 1[b1]	1.7 ± 0.2[c1]	↔		–	76 ± 12[e1]	↔	12.3 ± 1.3[f1]	↔	1.39 ± 0.53[g1]	↔
	120h	MEP 4 ± 1[b1]	1.7 ± 0.2[c1]	↔		–	77 ± 13[e1]	↔	12.9 ± 0.9[f1]	↔	1.55 ± 0.71[g1]	↔
	0h	MBP <LOD[b1]	NM	–	NM	–	NM	–	NM	–	NM	–
	1h	MBP <LOD[b1]		–		–		–		–		–
	2h	MBP <LOD[b1]		–		–		–		–		–
	3h	MBP <LOD[b1]		–		–		–		–		–
	4h	MBP <LOD[b1]		–		–		–		–		–
	24h	MBP <LOD[b1]		–		–		–		–		–
	96h	MBP <LOD[b1]		–		–		–		–		–
	120h	MBP <LOD[b1]		–		–		–		–		–

(*Continued on next page*)

Table 2: Magnitude and Variability of Phthalates in Human Biologic Fluids and Associated Thyroid Hormone Concentrations.[¥] Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients And Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study *(Continued)*.

		Phthalates Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites										
		(μg g^{-1} C.) [b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]		
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
	Young men-Exposure Week [26, 26 ± 4, 24 ± 2]												
	0h	MEP 7 ± 1[b1]	1.6 ± 0.3[c1]	↔	NM	–	74 ± 13[e1]	↔	12.5 ± 1.7[f1]	↔	1.50 ± 0.84[g1]	↔	
	1h	MEP 698 ± 69[b1]	1.6 ± 0.3[c1]	↔		–	75 ± 15[e1]	↔	12.6 ± 1.7[f1]	↔	1.30 ± 0.68[g1]	↔	
	2h	MEP 1001 ± 81[b1]	1.6 ± 0.2[c1]	↔		–	74 ± 15[e1]	↑**	12.5 ± 1.5[f1]	↔	1.23 ± 0.66[g1]	↔	
	3h	MEP 990 ± 68[b1]	1.6 ± 0.2[c1]	↔		–	73 ± 13[e1]	↔	12.6 ± 1.6[f1]	↔	1.27 ± 0.83[g1]	↔	
	4h	MEP 880 ± 75[b1]	1.6 ± 0.3[c1]	↔		–	74 ± 11[e1]	↔	12.6 ± 1.8[f1]	↔	1.30 ± 0.75[g1]	↔	
	24h	MEP 23 ± 3[b1]	1.6 ± 0.3[c1]	↔		–	74 ± 12[e1]	↓**	12.3 ± 1.5[f1]	↓***	1.50 ± 0.64[g1]	↔	
	96h	MEP 61 ± 11[b1]	1.7 ± 0.3[c1]	↔		–	77 ± 13[e1]	↔	12.9 ± 1.6[f1]	↑**	1.64 ± 0.68[g1]	↑***	
	120h	MEP 44 ± 11[b1]	1.7 ± 0.3[c1]	↔		–	79 ± 16[e1]	↔	13.1 ± 1.7[f1]	↔	1.67 ± 0.86[g1]	↔	
	0h	MBP <LOD[b1]	NM	–	NM	–	NM	–	NM	–	NM	–	
	1h	MBP 11 ± 2[b1]		–		–		–		–		–	
	2h	MBP 33 ± 5[b1]		–		–		–		–		–	
	3h	MBP 44 ± 5[b1]		–		–		–		–		–	
	4h	MBP 51 ± 6[b1]		–		–		–		–		–	
	24h	MBP 8 ± 1[b1]		–		–		–		–		–	
	96h	MBP 16 ± 2[b1]		–		–		–		–		–	
	120h	MBP 11 ± 2[b1]		–		–		–		–		–	
5	[74] Meeker et al., 2007 (USA)												
	Fertility study men [408, 36.2 ± 5.3, 27.8 ± 4.5]	MEP 158.0[a, b2]	96.0	↑	NM	–	NM	–	1.20	↓	1.43	↑	
		MBP 17.0[a, b2]		↓		–		–		↑		↑	
		MBzP 8.16[a, b2]		↑		–		–		↓		↑	
		MEHP 7.95[a, b2]		↓**		–		–		↓		↑	
		MEHHP 48.9[a, b2]		↓		–		–		↑		↑	
		MEOHP 32.9[a, b2]		↑		–		–		↑		↑	
		MEHP% 10.0[a, b2]		↓		–		–		↓**		↑	

[¥] Refer Table 1 footnotes for notations.

Table 3: Magnitude and Variability of Polybrominated Diphenyl Ethers in Human Biologic Fluids and Associated Thyroid Hormone Concentrations.[¥] Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients and Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study.

		Polybrominated Diphenyl Ethers and Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites										
		(μg g^{-1} C.)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]		
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
Polybrominated Diphenyl Ethers (PBDE)													
1	[114] Wang et al., 2010 (China)												
	Occupational exposure	BDE-209 58 ± 59[b3] **	10.7[a]	–	2.72[a]	–	7.76[a]	–	0.93[a]	–	1.11[a] ***	–	
	[239, 49.72[a], NM]	BDE-77 59 ± 109[b3] ***		–		–		–		–		–	
		BDE-85 130 ± 130[b3] ***		–		–		–		–		–	
		BDE-126 69 ± 208[b3] ***		–		–		↑**		–		–	
		BDE-205 10 ± 16[b3] ***		–		–		↑****		–		–	
		BDE-203 24 ± 60[b3] ***		–		–		–		–		–	
		∑PBDE 350 ± 582[b3]		–		–		–		–		–	
	Nonoccupational exposure	BDE-209 93 ± 198[b3] ***	10.3[a]	–	2.54[a]	–	7.25[a]	–	0.85[a]	–	1.06[a]	–	
	[93, 49.7[a], NM]	BDE-7 102 ± 223[b3] ***		–		–		–		–		–	
		BDE-85 148 ± 316[b3] ***		–		–		–		–		–	
		BDE-126 57 ± 101[b3] ***		–		–		–		–		–	
		BDE-205 7 ± 13[b3]		–		–		–		–		–	
		BDE-203 81 ± 215[b3] ***		–		–		–		–		–	
		∑PBDE 488±1066[b3]		–		–		–		–		–	

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Table 3: Magnitude and Variability of Polybrominated Diphenyl Ethers in Human Biologic Fluids and Associated Thyroid Hormone Concentrations.[¥] Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients and Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study. *(Continued)*

		Polybrominated Diphenyl Ethers and Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites									
		(μg g^{-1} C.)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]	
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
	Control group [116, 49.7[a], NM]	BDE-209 41 ± 43[b3]	11.9[a]	–	2.88[a]	–	7.69[a]	–	0.99[a]	–	1.43[a]	–	
		BDE-7 37 ± 33 [b3]		–		–		–		–		–	
		BDE-85 66 ± 69 [b3]		–		–		–		–		–	
		BDE-126 21 ± 35 [b3]		–		–		–		–		–	
		BDE-205 10 ± 14 [b3]		–		–		–		–		–	
		BDE-203 13 ± 18 [b3]		–		–		–		–		–	
		∑PBDE 187 ± 212 [b3]		–		–		–		–		–	
2	[120] Mazdai et al., 2003 (USA)												
	Pregnant women [15, 26.0[a], 36.0[a]]	BDE-47 28.0[a, b3]	NP	–	NP	–	9.5[a$]	–	1.2[a$]	–	NM	–	
		BDE-99 5.7[a, b3]		–		–		–		–		–	
		BDE-100 4.2[a, b3]		–		–		–		–		–	
		BDE-153 2.9[a, b3]		–		–		–		–		–	
		BDE-154 0.3[a, b3]		–		–		–		–		–	
		BDE-183 0.0[a, b3]		–		–		–		–		–	
		∑PBDE 37.0[a, b3]		↔		↔		↔		↔		–	
	Newborn Babies [12, day-1, NA]	BDE-47 25.0[a, b3]	NP	–	NP	–	9.5[a$]	–	1.0[a$]	–	NM	–	
		BDE-99 7.1[a, b3]		–		–		–		–		–	
		BDE-100 4.1[a, b3]		–		–		–		–		–	
		BDE-153 4.4[a, b3]		–		–		–		–		–	
		BDE-154 0.7[a, b3]		–		–		–		–		–	
		BDE-183 0.0[a, b3]		–		–		–		–		–	
		∑PBDE 39.0[a, b3]		↔		↔		↔		↔		–	

3	[126] Herbstman et al., 2008 (USA)											
	Infants—cord blood [289, day of birth, NM]	BDE-47 13.8[a, b3]	NM	–	NM	–	10.5[a, e3]	–	1.07[a, f4]	–	6.5[a, g2]	–	1.46 (T4),1.79 (FT4), 0.39** (ln TSH)
		BDE-100 2.3[a, b3]		–		–		–		–		–	2.14** (T4),1.69 (FT4), 0.36** (ln TSH)
		BDE-153 2.6[a, b3]		–		–		–		–		–	1.28 (T4),1.59 (FT4), 0.56 (ln TSH)
4	[127] Kim et al., 2009 (South Korea)											
	Infants [108, Day of birth, NM]	BDE-28 0.351[a, b4]	NM	–	NM	–	NM	–	16.0[a,f1]	↔	18.6[a]	↔	
		BDE-47 6.124[a, b4]		–		–		–		↔		↔	
		BDE-99 2.082[a, b4]		–		–		–		↔		↔	
		BDE-100 0.796[a, b4]		–		–		–		↔		↔	
		BDE-153 3.485[a, b4]		–		–		–		–		–	
		BDE-154 0.541[a, b4]		–		–		–		–		–	
		BDE-183 2.043[a, b4]		–		–		–		–		–	
		∑PBDE 8.227[a, b4]		–		–		–		↔		↔	
5	[135] Chevrier et al., 2010 (USA)											
	Pregnant women [270, 25.5 ± 5', NM]	BDE-17 <LOD[a, b3]	NM	–	NM	–	10.7 ± 1.6	–	0.83 ± 0.24	–	1.2 ± 1.7 [g4]	–	
		BDE-28 0.5[a, b3]		–		–		↑		↔		↓**	1.6
		BDE-47 15.0[a, b3]		–		–		↓		↔		↓**	1.8
		BDE-66 <LOD[a, b3]		–		–		–		–		–	
		BDE-85 <LOD[a, b3]		–		–		–		–		–	
		BDE-99 4.0[a, b3]		–		–		↓		↓		↓*	1.6
		BDE-100 2.4[a, b3]		–		–		↓		↓		↓***	2.1*
		BDE-153 2.1[a, b3]		–		–		↓		↑		↓**	2.4*
		BDE-154 <LOD[a, b3]		–		–		–		–		–	
		BDE-183 <LOD[a, b3]		–		–		–		–		–	
		∑PBDE 25.2[a, b3]		–		–		↓		↑		↓**	1.9

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Table 3: Magnitude and Variability of Polybrominated Diphenyl Ethers in Human Biologic Fluids and Associated Thyroid Hormone Concentrations.[¥] Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients and Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study. *(Continued)*

		Polybrominated Diphenyl Ethers and Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites										
		(μg g^{-1} C.)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]		
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
6	[42] Wan et al., 2010 (South Korea)												
	Pregnant women [26, 31 ± 4.7, 21.6 ± 4.2]	6′-OH-BDE47 0.0175 ± 0.0263	NA	–	NA	–	9.7 ± 1.8	–	NA	–	NA	–	
	Fetus [28, NM, 3.11 ± 0.46]	6′-OH-BDE47 0.0302 ± 0.0271	NA	–	NA	–	8.5 ± 1.7	↓	NA	–	NA	–	
7	[139] Lin et al., 2011 (Taiwan)												
	Pregnant women [54, 30.6 ± 5.01, 23.2 ± 4.53]	BDE-15 0.133[a, b3]	36.0[a, c3]	↓	1.39[a, d2]	↓	8.96[a, e3]	↓	1.15[a, f4]	↓	4.1[a, g3]	↓	
		BDE-28 0.101[a, b3]		↓		↓		↑		↓		↓	
		BDE-47 0.672[a, b3]		↓		↓		↓		↓		↓	
		BDE-99 0.724[a, b3]		↓**		↓***		↓		↓**		↓	
		BDE-100 0.174[a, b3]		↓		↓		↑		↓		↓	
		BDE-153 0.915[a, b3]		↓		↓		↑		↓		↓	
		BDE-154 0.100[a, b3]		↓**		↓**		↓		↓		↓	
		BDE-183 0.505[a, b3]		↓**		↓**		↓		↓**		↑	
		∑PBDE 3.490[a, b3]		↓		↓**		↓		↓		↓	

8	[144] Stapleton et al., 2011 (USA)										
	Pregnant women [137, NM, NM]	BDE-28 0.6[a, b3]	188.0[a]	–	2.71[a]	–	6.9[a, e4]	–	0.67[a]	–	1.28[a]	–
		BDE-47 18.87[a, b3]		↑		↑		↑**		↑**		↑
		BDE-66 0.6[a, b3]		–		–		–		–		–
		BDE-85,155 5.5[a, b3]		–		–		–		–		–
		BDE-99 4.61[a, b3]		↑		↑		↑**		↑**		↑
		BDE-100 0.6[a, b3]		↑		↑		↑**		↑		↑
		BDE-153 5.65[a, b3]		↑		↓		↑		↑		↓
		BDE-154 0.6[a, b3]		–		–		–		–		–
		∑PBDE-4 congeners 36.56[a, b3]		↑		↑		↑***		↑ **		↑
		4′-OH-BDE49 0.12[a, b3]		↓		↓		↑		↑		↑
		6′-OH-BDE47 0.13[a, b3]		↓		↑		↑		↑		↑
		∑OH-PBDE 0.33[a, b3]		↓		↑		↑		↑		↑
9	[161] Zota et al., 2011 (USA)											
	Pregnant women [25, 23 ± 7, NM]	BDE-28 2.4[a, b3]	NM	–	NM	–	12.8 ± 1.6	↓	1.0 ± 0.1	↓*	1.29 ± 0.67[g7]	↑
		BDE-47 42.1[a, b3]		–		–		↑		↓		↑*
		BDE-66 <MDL[a, b3]		–		–		–		–		–
		BDE-85 0.82[a, b3]		–		–		↑		↓		↑**
		BDE-99 9.8[a, b3]		–		–		↑		↑		↑
		BDE-100 8.96[a, b3]		–		–		↑		↓		↑
		BDE-153 16.5[a, b3]		–		–		↑		↑		↑
		BDE-154 <MDL[a, b3]		–		–		–		–		–
		BDE-183 <MDL[a, b3]		–		–		–		–		–
		BDE-196 <MDL[a, b3]		–		–		–		–		–
		BDE-197 <MDL[a, b3]		–		–		–		–		–
		BDE-201 <MDL[a, b3]		–		–		–		–		–
		BDE-203 <MDL[a, b3]		–		–		–		–		–
		BDE-206 <MDL[a, b3]		–		–		–		–		–
		BDE-207 1.54[a, b3]		–		–		↑		↑		↓***
		BDE-208 <MDL[a, b3]		–		–		–		–		–
		BDE-209 <MDL[a, b3]		–		–		–		–		–
		∑PBDE-5 congeners 82.9[a, b3]		–		–		↑		↓		↑*
		4′-OH-BDE17 0.016[a, b1]		–		–		↑		↔		↑

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Table 3: Magnitude and Variability of Polybrominated Diphenyl Ethers in Human Biologic Fluids and Associated Thyroid Hormone Concentrations.[¥] Statistical Associations Were Indicated With Positive (↑), Negative (↓), Nondistinct (↔), and Not Measured or Not Presented (–) Signs Inferred From Correlation/Regression Coefficients and Probability Values for Respective Pair of Plastic Additive Chemical/Metabolite and Thyroid Hormone Presented in Each Study. *(Continued)*

		Polybrominated Diphenyl Ethers and Metabolites	Serum Thyroid Hormones Levels and Relations with TDC and metabolites										
		(μg g^{-1} C.)[b]	T3 (ng dL^{-1})[c]		FT3 (pg mL^{-1})[d]		T4 (μg dL^{-1})[e]		FT4 (ng dL^{-1})[f]		TSH (μIU mL^{-1})[g]		
#	Study (Location) and Subjects [N, Age, and BMI (Mean ± SD)[a]]	Mean ± SD	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	Mean ± SD	Trend	OR
		5′-OH-BDE47 0.036[a, b1]		–		–		↓		↔		↑*	
		6′-OH-BDE47 0.023[a, b1]		–		–		↓		↓		↑	
		4′-OH-BDE49 0.010[a, b1]		–		–		↑		↔		↑***	
		∑OH-PBDE4 0.084[a, b1]		–		–		↓		↓		↑*	
10	[153] Roze et al., 2009 (Netherlands)												
	TH from pregnant mothers-35th week and related with BDE from theirs school age children [62, 32[a], NM]	BDE-47 0.9[a, b3]	0.8[a,c1]	↑**	NA	–	122[a,e4]	–	19.2[a,f5]	–	8.5[a,g5]	–	
		BDE-99 0.2[a, b3]		↑**		–		–		–		–	
		BDE-100 0.2[a, b3]		↑**		–		–		–		–	
		BDE-153 1.6[a, b3]		–		–		–		–		–	
		BDE-154 0.5[a, b3]		–		–		–		–		–	
11	[167] Gascon et al., 2011 (Spain)												
	Cord blood from pregnant mothers [88, 29.7 ± 4.3, 22.5 ± 3.4]	BDE-47 2.1[a,b3]	148.5[a1,c3]	–	NM	–	NM	–	1.0[a1]	–	1.6[a1,g6]	–	
		BDE-99 0.38[a,b3]		–		–		–		–		–	
		BDE-100 0.38[a,b3]		–		–		–		–		–	
	Kids at 4 years [244, NM, NM]	BDE-47 0.12[a,b3]	149.5[a1,c3]	↑	NM	–	NM	–	1.0[a1]	–	1.6[a1,g6]	–	
		BDE-99 0.12[a,b3]		–		–		–		–		–	
		BDE-100 0.12[a,b3]		–		–		–		–		–	
12	[170] Han et al., 2011 (China)												
	Children-electronic waste exposed site [195, 6–8 y, NM]	∑PBDE 664 ± 262 [b3]	NM	–	NM	–	NM	–	NM	–	1.88 ± 0.42**	↓**	
	Children-unexposed site [174, 6–8 y, NM]	∑PBDE 376 ± 262 [b3]	NM	–	NM	–	NM	–	NM	–	3.31 ± 1.04	–	
13	[171] Hagmar et al., 2001 (Sweden)												
	Men [110, NM, NM]	BDE-47 1.04[a, b3]	2.0[a, c2]	↔	5.2[a, d1]	↔	87.0[a, e2]	↔	13.0[a, f2]	↔	1.3[a, g1]	↓**	

14	[172] Bloom et al., 2008 (USA)											
		BDE-28 0.5[a, b3]	86.0[a]	–	NM	–	6.3[a, f3]	–	1.1[a]	↑	1.4[a]	↓	
	Sport fish Consumers [36, 39.5[a], 26.2[a]]	BDE-47 7.9[a, b3]		–		–		–		↑		↓	
		BDE-66 0.1[a, b3]		–		–		–		↑		↓	
		BDE-85 0.1[a, b3]		–		–		–		↑		↓	
		BDE-99 1.8[a, b3]		–		–		–		↑		↓	
		BDE-100 1.0[a, b3]		–		–		–		↑		↑	
		BDE-138 0.0[a, b3]		–		–		–		↑		↑	
		BDE-153 1.8[a, b3]		–		–		–		↑		↓	
		BDE-154 0.4[a, b3]		–		–		–		↑		↓	
		∑PBDE 15.0[a, b3]		–		–		–		↑		↓	
15	[136] Turyk et al., 2008 (USA)												
	Adult Male [308, 59.0[a], 29.2[a]]	BDE-47 0.11[a, b3]	99.0[a]	↓**	2.08[a]	↓	7.1[a]	↓	1.19[a,f3]	↑	1.55	↓*	
		BDE-99 0.03[a, b3]		↓		↓		↑*		↑***		↓	
		BDE-100 0.01[a, b3]		↓		↓		↑		↑		↓	
		BDE-153 0.03[a, b3]		↓**		↓**		↑**		↑**		↓	
		∑PBDE 0.26[a, b3]		↓		↓		↑**		↑**		↓	2.4 (any thyroid disease); 1.7 (hypothyroid disease); 5.7 (hyperthyroid disease)
16	[186] Dallaire et al., 2009 (Canada)	BDE-47 2.16[a1]	2.14 ± 0.33[c1]	↑***	NM	–	NM	–	15.5 ± 2.1[f1]	↑	1.18 ± 0.79	↓	
	Inuit adults [623, 36.8 ± 13.9, 27.4 ± 5.7]	BDE-153 2.05[a1]		↑		–		–		↑		↓	
17	[155] Meeker et al., 2009 (USA)												
	Fertility study men [24, 18–54 y, NM]	BDE-47 500[a, b5]	NP	↓	NM	–	NM	–	1100 (from graph)	↑**	NP	↑	
		BDE-99 838[a, b5]		↓		–		–		↑**		↑	
		BDE-100 180[a, b5]		↑		–		–		↑		↓	

¥Refer Table 1 footnotes for notations.

is often the case that biological sample contamination due to widespread BPA use in consumer and lab products further complicates human biomonitoring data interpretation [190].

3.1.1. General population

Subjects from the US National Health and Nutrition Examination Survey (NHANES) cross-sectional study (2007–2008) were selected to assess the relationships between urinary BPA, monoester phthalate metabolites, and thyroid status measurements [29]. Spot urine and single serum samples were collected from 1405 adults ($\geq$ 20 yrs) and 355 adolescents (12–19 yrs) and were analyzed for various urinary phthalate metabolites. Urinary metabolites and serum thyroid hormone levels, except for T3 and T4, were right-skewed and hence logarithmically transformed. Regression analysis was performed on unadjusted urinary TDC metabolites in investigating their associations with thyroid hormones. In both age groups, urinary BPA was inversely related to FT3 and T4, although statistically nonsignificant ($p > 0.05$) except for T4 in the adults group being marginally significant ($p = 0.049$) (Table 1). Limitations presented in this study were the ability to draw conclusions from a cross-sectional study design, use of spot urine sample, and the greater temporal variability of urinary BPA levels that have yielded weaker regression coefficients with respect to TH concentrations. In addition, the intra-class coefficient for urinary BPA levels was low in the range of 0.1 to 0.3 [30–32], suggesting that single urine spot may not be a good indicator for assessing a subject's BPA exposure. However, in contrast, a single spot serum sample performed better because the intra-subject variability was within narrow limits over time [33] and hence may be a suitable biological matrix for assessing chronic exposure of BPA. TDC, like BPA [34] and phthalates [35–37], were recently charged with altered thyroid signaling, leading to adverse effects on brain development. It was also speculated that thyroid health status was associated with insulin and diabetes conditions among adults exposed to these chemicals [38–40].

3.1.2. Pregnant women and infants

Sugiura-Ogasawara and colleagues [41] studied the association between BPA exposure and serum TSH in 45 women who had greater than three consecutive first-trimester miscarriages and 32 healthy women control subjects. BPA concentrations in patients' sera were significantly higher compared to those of healthy subjects (Table 1). No relationship was observed between urinary BPA with subjects body mas index (BMI). TSH and FT4 were measured but their levels not mentioned, since it was mentioned that there was no difference in urinary BPA levels between subjects with and without hypothyroidism. Urinary BPA levels were higher in subjects (4.39 ng ml^{-1}) who experienced miscarriages when compared to those with successful infant birth (1.22 ng ml^{-1}).

However, authors concluded that higher urinary BPA levels did not necessarily predict miscarriage.

Pregnant women (n = 26) in South Korea were recruited to study the transfer of BPA from mother to fetus [42]. BPA was shown to transfer through placenta and accumulates in developing fetus [43–47]. Observed serum T4 levels were higher in mothers compared with fetuses (Table 1), while they were not different between male and female fetuses. Serum BPA levels were similar between mother and fetuses (Table 1). BPA in maternal blood was shown to be higher than in cord blood [45,47], similar to this study [42]; except for [44] who reported contrasting observations. The relationship between BPA and thyroid hormones was not discussed, while it was speculated that BPA (partition coefficient logKow of 3.32) was transferred from placenta to fetus via transthyretin (TTR) protein, since chemicals with logKow in the range of −0.9 and 5.0 cross the placenta to the developing fetus [43]. Fetus growth largely depends on constant maternal supply of T4 during the first 16 weeks of gestation [48]. It is warranted that additional studies are needed on the effects of BPA transferring mechanism to fetus on T4 and other THs levels during fetus development.

3.1.3. Adults

Men (n = 167) from an infertility clinic were recruited to study the relationship between urinary BPA levels and serum TH along with other reproductive hormones [49]. Repeated urine sample collection was made for a second and third time from selected subjects between 1 week and 2 months, following the initial urine sample collection from all subjects. The assumption was that repeated measures might well represent BPA toxicokinetics because of its rapid metabolism and excretion. BMI showed significantly positive association with FT4 levels, while smokers showed higher serum FT3 and TSH levels when compared with nonsmokers. Timing and season of sample collection showed significant effects on TH and FT4 being significantly higher in the afternoon collected samples compared with those collected in the morning; however, no significant difference in the uncorrected BPA concentrations between the two time point collections. Specific gravity-corrected BPA levels were lower in winter when compared with those in spring, summer, or fall seasons. BPA showed nonsignificant inverse relationship with serum TSH and positive non-significant associations with serum T3 and FT4 levels (Table 1).

3.2. Phthalates

3.2.1. Pregnant women and infants

Pregnant women were recruited in a longitudinal study to identify the relationship between urinary phthalate metabolites and serum thyroid hormones in Taiwan [50]. Single serum and spot urine samples were collected from

76 pregnant women in their second trimester. With the exception of a single subject, no one else was occupationally exposed to plastics or cosmetics. Thyroid hormones (T3, T4, FT4, and TSH), and phthalate metabolites were analyzed using electrochemoluminescence immunoassay (ECLIA) and LC-ESI-MS/MS, respectively. Confounders such as smoking status, residential and occupational environment, and medical treatment during the first trimester did not show any significant effect on urinary phthalate levels. MBP, MEP, and MEHP levels were higher when compared with MMP and MBzP (Table 2), suggesting that the subjects were primarily exposed to DBP, DEP, and DEHP phthalates. Median urinary concentrations of MBP, MBzP, and MEHP (Table 2) were higher, while MEP was lower, when compared with the two reference studies from the United States with pregnant women and NHANES (1999–2000) subjects. The reference median urinary levels of MBP, MBzP MEP, and MEHP were 43, 12, 236, and 5 μg g^{-1} creatinine, respectively in US pregnant women [51] and 25, 15, 179, and 3 μg g^{-1} creatinine, respectively in the NHANES study (1999–2000) [52]. Thyroid hormone levels in the study subjects (Table 2) were comparable to reference range from the Taiwanese population [50], except for the lower FT4 levels in the study subjects indicating hypothyroidism. Creatinine-unadjusted (ng mL^{-1} urine) phthalate metabolites levels were used in statistical analyses for the reason that urinary creatinine could be highly diluted or concentrated during pregnancy and varied with each trimester. Spearman correlation showed significant decrease in T3, T4 levels with age ($p < 0.05$) and creatinine-adjusted MEHP showed significant decrease with BMI ($p < 0.05$), while contrasting trend was observed with creatinine-unadjusted MBP and MEP. MBP, a major phthalate metabolite, showed significant negative association with T4 and FT4, following adjustments for age, gestational age, etc. (Table 2). It was speculated that sample collections during the critical window of fetal development might have offered greater insight on thyroid hormone associations with other phthalate metabolites. MEP levels in urine were associated with dermal application and inhalation of personal care products usage [51,53]. Spot urine sample could be still considered as a representative for phthalate metabolite levels despite the false intra-variability even within days [54]. Specific care and monitoring is recommended for native phthalates analysis given the possibilities of cross-contamination from plastics equipment in a laboratory [55]. Timing of serum samples collection for TH analysis is crucial, since it was established that FT4 levels peak during the first trimester, followed by gradual decrease and stabilizing after the middle of second trimester (which is a critical window for sampling), and remains almost the same for the rest of pregnancy [56–58]. MBP in amniotic fluid was identified as a possible biomarker for fetal thyroid function [59]. Hence, urinary MBP shown in this study could be a proxy indicator of phthalates exposure during early pregnancy.

3.2.2. Children and adolescents

The relationship between 12 urinary phthalates metabolites and TH was extensively studied in Danish boys (n = 503) and girls (n = 342) aged between 4 and 9 years [60]. This is one of the very few studies that measured thyroid volume (mL) using ultrasound measurements and urinary iodine levels, both of which are relevant for understanding thyroid health. Children who displayed symptoms related to growth and those with puberty signs were excluded from the study. Spot urine and single blood sample were collected to analyze for phthalates metabolites and thyroid hormones using SPE-LC/MS/MS and electrochemoluminescence immunoassays, respectively. Phthalate metabolites analyzed were, with parent diester in parenthesis, MEP (DEP), MBP (DiBP, DBP), MBzP (BBP), MEHP, MEHHP, MEOHP, and MECPP (DEHP), MOP (DOP), and MiNP, MCiOP, MHiNP, and MOiNP (DiNP). $\sum$DEHP-metabolites were calculated by summing MEHP, MEHHP, MEOHP, and MECPP levels, which were corrected for molecular weights. Phthalate score was also calculated to estimate combined phthalate exposure by classifying the metabolites levels into quartiles and totaling their scores [60]. Phthalate metabolites levels were adjusted using creatinine data either by dividing with it or using its square root concentrations in the regression analyses. However, creatinine-unadjusted (crude analysis) suggested several significant association trends between phthalate metabolites and TH; more over the significant relations were prominent in girls compared to boys. Significant inverse relations were reported between several urinary phthalate metabolites and serum T3, FT3 levels in girls (Table 2). Similar trends were observed in boys as well, although nonsignificant, except for MBP with FT3 (Table 2). Phthalate scores showed significant inverse relation with T3, FT3, and T4 levels in girls; while $\sum$DEHP-metabolites showed significant inverse relation with only T3 and FT3 levels in the same sex group (Table 2). Significant negative correlations ($p < 0.05$) were observed between urinary phthalate metabolites such as MEP, MEOHP, MECPP, $\sum$DEHP-metabolites, and phthalates core with absolute values of height, weight, BMI, body surface area, and age [60]. No significant differences were observed between thyroid size and phthalates metabolites levels, given the observation that the thyroid size is regulated by multimetabolic variables and not necessarily represent a relation with urinary phthalate metabolites levels. Koch and colleagues [61] observed that the magnitude of phthalate exposures in children was higher when compared with that of adults. Phthalate metabolites levels observed in this study were in general comparable to those reported in other children studies [52,61–64]. MEP levels in this study child [60] were lower comparatively with other children studies [31,52]. Danish children showed higher urinary MBP levels [60], compared with children from the United States [52,63,64]; however, were comparable with levels observed in Swedish young adults [65] and German children [61]. These observations present the regional differences in chemical exposures and their excretion

that needs to be paid attention while make cross comparisons among studies. Insulin-like growth factor (IGF-I) levels were altered in children due to phthalates exposure [60,66], indicating the role of IGF-I affecting serum T3 levels given the knowledge that IGF-I is involved with the conversion of T4 to the biologically active forms of T3 [67,68]. Wolff and colleagues [69] observed an increased infant head circumference with phthalates exposure of their mothers during pregnancy. Inferences on relations using creatinine-adjusted urinary metabolites levels must be made with caution given the knowledge that creatinine excretion patterns vary widely being strongly correlated with age, height, weight, and body surface area [70], along with higher excretions in boys compared with girls [70]. Urine volume was influenced by age, thyroid hormones [71], and IGF-I [72], which in turn influences urinary metabolites levels making these relations vary particularly in the case of children subjects. In addition, children might get exposed to higher levels of phthalates relative to body size because of their relative higher food consumption and higher body surface area [73]. MEHP used as a potential urinary marker to determine phthalates exposure [74] was supported by the negative association with T4 in this study [60]. The authors supported the view that thyroid hormones might affect phthalates metabolism.

Meeker and Ferguson [29] showed that both monoester and oxidative metabolites of DEHP and DBP, such as MEHP, MEHHP, MEOHP, MECPP, MnBP, MiBP, and MCPP, were measured in the spot urine samples from the two age group subjects ($\geq$ 20 yrs and 12–19 yrs adolescents). Regression analyses with unadjusted urinary phthalates metabolite levels showed a significant inverse relationship between MEHP, MEHHP, MEOHP, and MECPP (all the monitored DEHP metabolites) with T4 in the adults group (Table 2). However, using adjusted levels with age, sex, BMI, serum cotinine, and urinaryiodine and creatinine resulted in more significant relations. Certain DEHP metabolites from the adults' age group showed significant inverse relations with both T4 and T3, and positive relation with TSH levels (Table 2). These findings led to the speculation that DEHP exposure primarily affected thyroid hormone synthesis, release, and transport processes, while the effect on the hypothalamus or anterior pituitary remained to be unseen [29]. Adolescents sample size was smaller compared with adults for inferring the associations' outcome. The positive association between DEHP urinary metabolites and serum T3 levels in the adolescent group could be due to residual confounding from high T3 levels until the onset of puberty [75]. Urinary MCPP, an oxidized metabolite of both DBP and Di-n-octyl phthalate (DOP), showed inverse association with certain thyroid hormones [29]. This observation is in accordance with other findings where DOP affected thyroid measurements in rats [76], associated with sodium/iodide symporter (NIS) gene expression in *in vitro* human thyroid cells [77], and found in well water of an endemic goiter area that was not iodine-insufficient [78].

3.2.3. Adults

Twenty six healthy young men were recruited in Denmark to study whether dermal application of a cream formulation containing phthalates, such as DEP and DBP-affected TH levels along with certain other reproductive hormones [79]. Men were chosen to avoid discrepancies in interpreting results as in the case of women with varying hormone levels during premenopausal stage as well as avoid posing pregnant women. Subjects received an almost full body topical application of a basic cream formulation without and with analytes of interest, DEP and DBP, at the rate of 2 mg cm^{-2} body surface area every day for five days during control and treatment week, respectively. Blood samples were collected at 0, 1, 2, 3, 4, 24, 48, 72, 96, and 120 hours; and the sera were analyzed for MEP, MBP monoester phthalates and T3, T4, FT4, TSH using SPE-LC/MS/MS and double antibody enzyme immunometric assay, respectively. MEP and MBP were not detected in serum prior to the treatment, which significantly increased to a maximum of 1001 and 51 μg L^{-1} in 2 and 4 hours of cream application for MEP and MBP, respectively. Their levels decreased within 24 hours but did not reach the observed levels of the control week group. There was no difference in T3 and TSH levels between 0 and 24 h time of collection among the control and treatment weeks, while T4 and FT4 decreased significantly during this period (Table 2). However, the authors attributed this to chance observations. In addition, lack of any changes in TSH levels validates their speculation of attributing the changes in other THs due to normal biological variations. Hydrophilic phthalates such as DEP showed highest rate of dermal absorption, while lipophilic phthalates such as DBP the least.

Biological samples from men ($n = 408$) in subfertile couples from a male infertility clinic study in the United States were analyzed for DEHP and TH levels [74]. A single nonfasting blood sample and spot urine were collected and analyzed for TH, and phthalate monoester and oxidative metabolites using microparticle enzyme immunoassay and SPE-HPLC/isotope-dilution MS techniques. Subjects included in this study were free from using hormone medications and others that could alter thyroid axis. Age showed significant association with T3 and FT4 ($p < 0.05$), while BMI showed positive association with T3, TSH, MBzP, MEHHP, and MEOHP ($0.01 < p < 0.05$). Smoking status showed a trend of higher median T3 and TSH levels in smokers compared to nonsmokers, while no trend was observed with T4. Time of urine sample collection had an effect on MEHP analysis, with higher levels being observed in afternoon samples compared with the morning collection. Regression models adjusted for age, BMI, smoking, and the time of collection showed a significant negative relation between MEHP with T3 and MEHP with FT4 ($p < 0.05$) (Table 2). Oxidative metabolites of the parent diester DEHP, viz., MEHHP, and MEOHP were highly correlated. This would be the first report on probing the metabolism of parent diester phthalates and the role of phthalate monoester

and oxidative metabolites in influencing thyroid hormone status. Pathways of DEHP metabolism in humans determined the extent of excretion of monoester and oxidative metabolites, which in turn dictated their effect on fluctuations of TH levels. Meeker and colleagues [74] proposed a possible reverse pathway in which thyroid health of an individual might affect the metabolism of DEHP and thereby influence the metabolite levels excreted in urine. In case of hormone studies, at low exposure doses of environmental contaminants such as DEHP a nonlinear relation might occur between the metabolites (such as MEHP) and thyroid hormones (such as T3 and FT4) when categorized as quintiles [74]. Hence, regression methods that are based on linearity may not be suitable in such cases, as also supported by others [80]. MEHP could be used as a potential marker to understand DEHP metabolism and excretion in humans [74]. Further studies are needed to identify the pathways in which plastic additives may alter thyroid function. Early urine collection, within 12 hr following DEHP exposure might have higher levels of its monoester metabolite, MEHP; while a later sample contained more oxidative metabolites such as MEHHP and MEOHP [74]. Hence timing of urine sample collection influences the relations in any particular study. The intra-class correlation coefficient for phthalates metabolites levels in urine samples collected repeatedly for weeks to months ranged from 0.2 to 0.7 [31,81–83]; suggesting that one urine sample per person may not be a representative of phthalates exposure, since they get metabolized quickly with large inter-subject variability patterns [29].

3.3. Polybrominated Diphenyl Ethers (PBDE)

3.3.1. General population

Ingestion of PBDE via contaminated food is the primary source of exposure, followed by either or all inhalation, ingestion, skin uptake of PBDE-loaded house dust released from furniture, and electrical appliances [84–92]. A comprehensive US-based exposure assessment suggested that about 82% of total PBDE daily body burden may originate from house dust, while dietary intake was a minor contributor to daily dose [90]. PBDE metabolites were shown to alter and/or interfere with hypothalamic-pituitary-gonadal axis functioning [93–99]. House dust was proposed to be an appropriate marker for long-term environmental exposure to PBDE given their varying half-life in biological matrices ranging from months to years [100].

3.3.2. Occupationally exposed population

Lower-occupational exposure to PBDE in humans has shown long half-lives ranging from weeks to months [101,102]. In addition, lower order bromine congeners tend to have longer half-lives in humans as they accumulate in vital organ tissues [103–105]. Both PBDE and their metabolites were shown

to affect thyroid functioning [106], either via competitive binding to thyroid receptors [107,108] and/or attaching to serum transport proteins [109]. Despite the ban and voluntary cessation of manufacturing penta- and octa-BDE mixtures [110], it was speculated that body burdens of PBDE from previous years doubled every 5 years as of the year 2000; while the levels in US populations were about 20 times higher than those in Europe [111–113].

Occupational exposure to PBDE was studied in 239 workers, 93 subjects that were non-occupationally exposed at an electronic waste (e-waste) recycling area and 89 healthy controls from a green plantation area in China [114] (Table 3). Recycling e-waste activities were separating, burning, and leaching with poor personal protection protocols. Occupational exposure parameters such as duration of exposure and working years at the dismantling site showed significant positive relations with PBDE. Occupational exposed subjects had lower TSH ($p < 0.001$) when compared with those of the control group. Age and race showed no significant relation with TH levels, while BMI showed a weak positive relationship with serum TSH concentrations in serum. Use of protective mask positively intervened with sera PBDE levels, suggesting that inhalation was the primary exposure route at this recycling site [115]. BDE-126 and -205 congeners in sera showed significant positive association with T4 levels (Table 3). Total PBDE in exposed group (median value of 190 ng g^{-1} lipids) was higher than in control group (median, 122 ng g^{-1} lipid). BDE-197, −207, and −208 were reported to be significantly higher in workers at an e-waste dismantling site compared with unexposed subjects [116]. High levels of PBDE were reported in milk, placenta, and hair samples of women working at the e-waste recycling site compared with subjects from a control area [117]. A similar study [118] reported no significant relationship between PBDE and TH, such as T3, FT4, and TSH, except for BDE −28, −153, and −183 congeners showing a weak positive relationship with FT4; however, the sample size of the study was small ($n = 11$). Similar trendline between PBDE and TH was reported [119], showing high TSH levels in electronic waste workers compared with control subjects.

3.3.3. Pregnant women and infants

Mazdai and associates [120] reported for the first time elevated PBDE levels in blood samples for US pregnant women-fetus pairs. BDE-47 was predominantly detected (53%–64%) among the six PBDE congeners in pregnant mother sera (Table 3). Strong positive correlation was observed between mother and fetus samples for total PBDE. No significant relations were observed between age and BMI with maternal sera PBDE, and for infant birth weight with fetuses PBDE levels. In addition, no relation was observed between PBDE levels and T3, FT3, T4, and FT4 in both maternal and fetuses sera (Table 3). Strong positive correlation between maternal and fetal sera

PBDE levels indicated biochemical transfer of PBDE from mother to child, despite that the small sample size (n = 9 babies) warranted further investigation. Sweden banned use of lower BDE congeners by July 2003 given the observation in increase of sera PBDE by 9-fold between 1977 and 1999 [121]. Voluntary phase-out of penta-BDE may be the reason for lowered PBDE levels in milk samples from Swedish women [122]. PBDE levels in pregnant women and fetal sera were greater in a US study by up to 30 times [120] when compared with PBDE levels observed in a Swedish study [123]. Despite greater occurrence of BDE-99 in air (constituting 35% of total PBDE) [124], only 15%–19% levels were measured in human sera [120]. Similarly, BDE-183, which was a major constituent of octa-BDE mixture [125] was not detected in all sera samples [120]. This may be due to differences in bioavailability of the congeners, duration of exposure due to differences in vapor pressure, and/or selective transformation to metabolites of higher potency.

Relationships between PBDE and TH in cord blood of infants were investigated by [126] (Table 3). Linear regression analyses showed weak associations of BDE-100 and BDE-153 with T4 in cord blood. Infants delivered by spontaneous unassisted vaginal delivery (SUVD) showed a significantly inverse relationship between PBDE and T4 levels. Upon adjusting the models for infant sex, gestational age, pregnant mother's age, mother's race, pregnant mother's BMI, and smoking preference; significant odds ratios (ORs) were observed between BDE-47 and BDE-100 with TSH, and BDE-100 with T4 levels in cord blood (Table 3), suggesting higher levels of BDEs resulted in reduced likelihood of having higher TSH and T4 levels, respectively. Samples collected from SUVD-born infants at the time of birth, about 2 days after birth, and about within a month from birth showed similar associations between PBDE and T4 levels. Prenatal exposures to PBDE may result in lower T4 levels in infants' cord blood as well as in the subsequent neonatal developmental stage. Iodine status was not measured, which could be another good indicator for thyroid hormone metabolism in relation to PBDE exposure. Timing of sample collection is important given the fact that thyroid hormones surge during birth influencing the interpretation of the results.

No significant relationships were observed between PBDE congeners such as BDE-28, −47, −99, and −100 as well as FT4 or TSH in infants' cord blood (n = 108) measured in South Korea [127] (Table 3). Mean $\sum$PBDE levels in umbilical cord blood samples of infants from several countries were about 8.4 ng g^{-1} lipid in South Korea [127], 1.7 in Sweden [123], 7.9 in Netherlands [128], 6.2 and 13 in Spain [129 and 130, respectively], 3.9 in China [131], 2.2 in Faroe Islands [132], 52.6 in the United States [133], and 1.8 in Japan [134].

The relationship between serum PBDE and THs levels in pregnant women (n = 270) in their 27th week of gestation was also studied [135] (Table 3). Unadjusted regression models showed significant negative relations between BDE-28, −47, −99, −100, −153, and $\sum$PBDE with TSH (Table 3). Non-monotonic

exposure relationships were noticed between BDE congeners and TSH when categorized in quartiles. Increased BDE-100 and −153 exposures resulted in a significant increase in odds ratio (OR) for subclinical hyperthyroidism, which could be associated with decreased TSH (Table 3). Lower molecular weight BDE congeners tend to persist because of their longer half-lives estimated in the range of 2 to 12 years in human tissues [105]. Turyk and colleagues [136] reported increased PBDE exposure resulted in increased OR for serum thyroglobulin, which was associated with Graves's disease. Grave's disease may be the major cause for hyperthyroidism in pregnant women [56,137]. Hence PBDE exposure was related to subclinical hyperthyroidism [135]. Hyperthyroidism in pregnant women may lead to increased miscarriage rates, premature births, etc. [138]. Hydroxylated PBDE may bind to thyroid receptors because of their structural similarities with T3 and T4 hormones and thus inhibit TSH release from pituitary gland [108].

Hydroxylated PBDE, the major PBDE metabolites in serum, could easily cross the placenta via their transfer from pregnant mothers to infants. Such processes could therefore impact the physiology and metabolism of TH in infants [42] (Table 3). Both maternal sera and fetal cord blood showed very high levels of 6-OH-BDE-47 for all studied hydroxylated PBDE (Table 3). T4 levels in fetal sera were significantly lower upon OH-PBDE exposure. Seafood could be the major source of 6-OH-BDE-47 exposure in the South Korean women. 6-OH-BDE-47 show competitive binding with transthyretin (TTR), which determines accumulation of the hydroxyl BDE, binding and transfer of T4.

Measurements of PBDE and TH in cord blood of Taiwanese infants (n = 54) were undertaken to better understand prenatal exposure and placental transfer of brominated compounds [139] (Table 3). Pregnant women who participated in the study provided information on social and economic conditions, smoking, eating and drinking behavior, medical history, and possible exposure to PBDE via occupational or non-occupational routes (electronics use and transportation). All congeners, BDE−15, −28, −47, −99, −100, −153, −154, and −183, were above limit of detection (LOD) in at least 50% of the study sera samples. Negative associations were observed between several BDE congeners and thyroid hormones such as T3, FT3, T4, FT4, and TSH; while only certain relations were statistically significant (Table 3). Following confounding and multiple linear regression stepwise analysis, significant negative relations were noticed between BDE-100 and T4/T3, BDE-153 and −183 with FT3, and BDE-154 with T3. No significant relationship was observed between BDE-47 and thyroid hormones. A serious limitation of the study could be the small sample size, and hence the authors suggested a larger and longitudinal epidemiological study for future research. Body burden of PBDE in infants was calculated following Schecter's approach [140] and was estimated to about 14.5 ng $\sum$PBDE in this study [139]. PBDE in cord blood were significantly higher in

infants with unhealthy birth outcomes such as low birth weight, premature delivery, etc., when compared with PBDE levels of healthy infants [141]. Higher cord blood PBDE was significantly associated with decreased scores for mental and motor neurodevelopment in children between 1 and 4 years [142]. Higher levels of PBDE in breast milk were significantly associated with lower birth outcomes [143].

Pregnant women (n = 140, and > 34 weeks of pregnancy) were recruited to find associations between PBDE, their metabolites, and TH levels [144] (Table 3). Total PBDE (sum of BDE−47, −99, −100, and −153) showed significant positive association with T4 and FT4 levels (Table 3). Inverse relation was observed between 4'-OH-BDE-49 and T3, FT3, although not significant (Table 3). Each PBDE was positively correlated with the respective OH-BDE metabolites, except for BDE-99 and 6-OH-BDE-47 [144]. This could be perhaps true for two speculated reasons: (i) 6-OH-BDE-47 may not be a BDE 99-specific metabolite originating from other possible sources [145] and (ii) it may be that BDE-99 gets rapidly metabolized when compared with BDE-47 and −153 [146–151]. Significant associations were observed between PBDE levels in pregnant mother and cord blood tissues with infants showing symptoms, such as cryptorchidism, underweight at birth, and brain developmental issues [142, 143, 152, 153]. Exposure in women as well as in men was associated with altered hormones and fecundability [154, and 155, respectively]. Positive relations were observed between PBDE and T4 [144], which were in contrast to animal studies that showed negative relation with T3 and T4 levels [156–158]. Hydroxylated PBDE had significantly higher binding affinity toward thyroid hormone transporters found in serum compared to parent congeners observed in *in vitro* studies [109,159]. In particular, 4'-OH-BDE 49 displayed higher binding affinity to transthyretin, a thyroid hormone serum transporter [160]. Hence it may be speculated that the competing PBDE metabolites for binding sites on the thyroid hormone transporters results in liberating free T4 [144].

A cross-sectional study was carried out in California (USA) to identify possible associations between PBDE exposure and thyroid function in pregnant women [161] (Table 3). PBDE congeners were classified into lower-brominated PBDE (BDE-17 to -154), higher-brominated PBDE (BDE −183 to −209), and OH-PBDE metabolites to find associations. Interrelations between PBDE and hydroxylated (OH)-PBDE were also studied in relation to TH status. Age and race did not have any effect on TH levels in general, except for a negative association with T4. Sum of lower order brominated congeners and hydroxylated metabolites showed significant positive association with sera TSH levels (Table 3). Negative association was reported between BDE-207 and TSH (Table 3). Structure of BDE congener determined its effect on thyroid function given the observations that BDE-209 had no binding effect on TTR [162] and did not yield hydroxylated metabolites in *in vitro* human liver cells [151]. PBDE were seven times higher in Mexican-American children in California

compared to their counterparts in Mexico [163]. OH-PBDE may disrupt thyroid function to a greater extent compared with their parent congeners, since OH-PBDE binds strongly to both TTR and TBG when compared with the respective parent compounds [159,164]. In addition, OH-PBDE and not their parent congeners have shown the ability to bind to thyroid hormone receptors such as TRα and TRβ [165,166].

3.3.4. Children and adolescents

School children aged 5 to 6 years (n = 62) were examined with respect to their behavior performance characteristics based on PBDE levels in their mothers' serum during pregnancy and thyroid hormones in umbilical cord serum [153]. BDE-47, −99, and −100 were positively associated with T3 concentrations (Table 3), but the same PBDE congeners were negatively associated with sustained attention performance in the study school children whose mothers were exposed to PBDE.

Children at age 4 participated in a motor and cognitive abilities test for assessing their neurodevelopment status, followed by providing blood samples for PBDE and TH analyses [167]. In addition, their mothers during pregnancy also participated in a survey and provided cord blood samples for the same analyses. The objective of this study was to identify relationships between pre-, and postnatal PBDE levels and children's' neurodevelopmental scores. BDE−47, −99, and −100 (tetra and penta PBDE) showed longer half-lives (years) in animal studies [168]. Hence the PBDE measured in children at age 4 could be from historic exposures and hence were collectively termed postnatal exposure. Similarly pregnant mothers exposed to PBDE prior to birth and that cumulative exposure window was termed as prenatal exposure. This was supported by the observation that PBDE levels in pregnant women sera (from 10–13 weeks of pregnancy) were similar to those in cord blood at the time of giving birth, following lipid normalization [169]. PBDE levels in cord blood were higher in cord blood compared to those in respective children at age 4 (Table 3). BDE-47 was the predominant congener in cord blood samples, and their levels showed a weak negative association with neurodevelopmental scores of the respective children. However, significant association was observed between BDE-47 exposure during the postnatal period and higher probability of attention deficit symptoms in children. No significant associations were observed between PBDE and TH levels in cord blood sera (Table 3), except for speculative evidence between BDE-47 congener and T3 levels in children. Strong negative associations between cord blood PBDE levels and cognitive function of children at age 4 were observed in a US study [142], while no such relations were observed in children between 5 and 6 years in a Dutch study [153]. The differences in prenatal and postnatal exposures to PBDE in studies were because of the strict prohibition of certain brominated compound usage in the European Union.

Children from an electronic-waste recycling site in China were tested for ∑PBDE and TSH in blood samples and were compared with control children subjects from a non e-waste site [170]. Sera ∑PBDE levels were significantly higher in children from e-waste site compared to those from a control area. TSH levels were significantly lower in the former subjects (Table 3). A negative association was observed between sera ∑PBDE and TSH [170].

3.3.5. Adults

BDE-47 in sera from male fish consumers in Sweden (n = 110) was measured to investigate possible associations with fluctuations in thyroid hormones [171]. Subjects had varying fish consumption patterns (0–32 servings per month) and a significant negative relationship was observed between BDE-47 and TSH levels; however, no such relationship was observed with the rest of thyroid hormones (Table 3).

Bloom and associates [172] studied the relationship between dietary exposures of PBDE with thyroid function in sportfish anglers. Sportfish species in the North American Great Lake were shown to have high levels of PBDE [173,174]. Gill and colleagues [175] proposed that about half the average daily human uptake of PBDE originated from fish consumption. Plasma levels of PBDE and thyroid hormones were measured in 36 licensed Lake Ontario anglers in a cross-sectional study [172]. Most of the PBDE congeners measured were below limit of detection (LOD), except for BDE-47, 100, and 153 (Table 3). Age showed significant inverse correlation with BDE-99, and showed a negative trend with ∑PBDE. Due to suspected degradation of T3 and T4 in blood samples during storage [176], only FT4 and TSH levels were used in identifying relations with plasma BDE levels. Nonsignificant positive association was observed between ∑PBDE and FT4, while there was a negative relationship with TSH levels (Table 3). These findings support earlier studies on PBDE levels in human blood in relation with thyroid hormones [118,120,177]. BDE-47 was the predominant congener measured in this study, which was consistent with findings by [118,120, and 171]. Similar to [118] dietary exposure findings, BDE-99 and 153 were the predominant congeners in the studied human sera. T3 and T4 levels in several subjects were below LOD compared with a similar study with Great Lakes sportfish anglers [178] and representative study subjects [179]; which indicated a possible degradation of these analytes in study samples. Age and gender relationships with certain PBDE congeners were in accordance with dietary exposure estimates based on demography [180]. The drawback of this study was that PBDE metabolites were not measured which are demonstrated to have more biological relevance than parent compounds [108]. The cross-sectional nature of this study [172] gives a snap shot of relations at a given time point, but excludes the possible associations between the initial BDE exposures and subsequent thyroid compensatory metabolisms [181]. The observed positive relationship between PBDE congeners and FT4

could be an artifact from the small study sample as suggested by the authors, since the results were contrasting to the inverse relationship reported in animal studies reported in literature [182–184].

Adult male (n = 308) sport fish consumers provided serum samples to investigate possible associations between PBDE and thyroid hormones concentrations [136]. ∑PBDE were significantly (positively) associated with T4 and FT4 (Table 3). BDE-47 was the major PBDE congener that showed significant negative association with T3 and TSH [136] (Table 3). Authors speculated that PBDE effects on thyroid may be modified by fish consumption. PBDEs share similar chemical structures with T4 and T3 [162]. Hence, it is likely that PBDE interfered with thyroid metabolism via alterations in the activity of the hypothalamus-pituitary-thyroid axis [185]. Adults (n = 623) who were exposed to high levels of PCBs via seafood were selected to probe relations between plasma PBDE and serum thyroid hormones [186]. BDE-47 showed significant positive association with T3 [186] (Table 3), which was deemed not significant after adjusting for fish consumption.

Twenty four men aged between 18 and 54 yrs, from infertile couples either due to the male partner, or female, or both participated in a reproductive health study measuring PBDE in sera and house dust samples [155]. T3 and FT4 levels were normally distributed and untransformed, while TSH and PBDE levels were log transformed for inclusion in the regression analyses. Regression coefficients were presented as percent change in each TH level compared to the study population median. Analyzed BDE congeners viz., BDE-47, 99, and 100 were highly correlated suggesting same source(s) of origin within a home. Significant positive associations were observed between house dust levels of BDE-47, 99, and 100 with serum FT4 levels from the adjusted regression models (Table 3). With each interquartile range increase of PBDE levels in house dust, a significant 4% increase in serum FT4 was observed [155]. This was the first study to confirm the relationship between house dust-originating PBDE and serum hormone levels. These study findings are in accordance with other human studies where PBDE levels were positively associated with serum FT4 levels in adult men [136,172]. However, certain animal studies have consistently reported negative associations between PBDE and T4 levels from PBDE exposures during the developmental stage [99,187]. These observations suggest that PBDE's effects on T4 vary from developmental to adulthood stages of life. The authors speculated that PBDE might affect the hypothalamus or pituitary activities in adult men, according to recent findings from animal studies [188,189]. The authors concluded that additional large-scale human studies are needed to confirm the relationship between house dust PBDE levels and thyroid hormones, via inclusion of other PBDE congeners and/or flame retardants [155] (Table 3).

4. CONCLUSIONS

This collective review on thyroid disrupting chemicals (TDC), is the first that integrates information from human studies reporting relationships between TDC and serum thyroid hormones. The term thyroid disrupting chemicals was coined in this review for those synthetic everyday consumer chemicals adversely impacting thyroid gland physiology, and possibly disrupting hormonal homeostasis in other endocrine systems as well (central nervous system, reproduction). This review study focused on TDC like PBDE, phthalates, and BPA because of (i) their very high volume-based use in consumer and industrial processes and products and (ii) their inclusion in a relatively extensive number of toxicological studies when compared with other emerging TDC.

The primary documented role of TDC in adversely impacting thyroid health was manifested in the reduction of the magnitude of circulating TH concentrations. TDC in serum may interfere with biochemical pathways of T4 and T3 as they enter circulation where specific proteins bind to them, increasing their bioavailability upon delivery to thyroid hormonal receptors. As a result, reductions in produced TH could trigger hypothalamus-pituitary axis to induce T4 synthesis in the thyroid gland. Three major mechanisms of TDC interference with thyroid gland activities were considered to be [7,10,11,16,191,192]: (i) direct interference with thyroid gland in decreasing TH production,(ii) increased hepatic excretion of T4 via uridine diphosphate glucuronidation where activated nuclear receptors in hepatocytes produce enzymes catalyzing TH elimination via deiodination processes into either serum or bile, and (iii) TDC-induced T4 displacement from binding proteins, leading to hepatic elimination. It has been shown that the anticipated behavior of increased serum TSH concentration due to reduction in T4 or FT4 may not be always the case, including scenarios where TDC-inducing T4 or FT4 decrease in serum was not associated with a concomitant change in TSH [11]. Current knowledge lacks solid data ascribing TDC and TH concentration fluctuations to disease process or specific end points.

This review also reported the sporadic prevalence of subclinical thyroid disease (SCTD) in sensitive subpopulations showing malfunctioning of the HPT axis associated with TDC and/or their metabolites. Approaches relying on the identification of population-based subclinical changes in TH with respect to TDC exposure might lead to better design of TDC exposure prevention and intervention measures. There still remains a lack of consensus in translating incident rates of SCTD to the development or progression of a disease from population screening studies [193–195]. The primary reason for this could be that SCTD was characterized by abnormal serum TSH levels, while the range for normal TSH levels remains yet to be established from clinical studies [196,197]; at the same time, TSH reference cut-off limit varies among individuals due to their physiologic differences in HPT axis activity [20].

Our collective findings may qualitatively suggest that plastic additives, i.e., TDC, commonly used in everyday products, such as BPA, phthalates, and PBDE, have mixed significant (alpha = 0.05) associations with thyroid hormones (either positive or negative sign of the respective correlation or regression coefficients in the presented studies). Non monotonic trends observed in low-dose effects of exogenous hormones, like TDC as suggested by Vandenberg and colleagues [198], requires careful interpretation of measured outcomes and relationships between TDC and natural TH in epidemiologic studies. The mixed results among the reviewed studies could be ascribed to differences in study design such as cross-sectional, prospective, or retrospective studies, frequently encountered small sample size, TDC sample preservation and collection of time, age, BMI, race, and other effect modifiers. However, it was shown that specific subpopulation groups, such as pregnant women and children, were highly susceptible to TDC exposures as expressed via perturbations in thyroid hormone concentrations (thyroid dysfunction).

Because of greater lipophilicity and longer half-lives corresponding to certain TDC, like PBDE, it was warranted that long-term, rather than short-term exposures should be considered during derivations of population risks associated with subclinical thyroid health outcomes (hypothyroidism, hypothyroxinemia). Future studies should undertake comprehensive meta-analyses to elucidate pooled summary TDC effect estimates on thyroid health as it is typically expressed via thyroid hormonal measurements. Since BPA, PBDE, and phthalates are not the only potent TDC that could influence thyroid health, it is foreseen that additional studies should be undertaken focusing on better designed exposure assessment protocols for mixtures of emerging TDC. Overall, a lack of consistency and specificity in findings among the reported studies was observed, resulting in mixed results and inconclusive statements associated with the speculated TDC effects on a population's subclinical and clinical thyroid health outcomes.

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