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ORIGINAL ARTICLE

Associations between endocrine disruptor contamination and thyroid hormone homeostasis in Belgian type 1 diabetic children

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Abstract

Purpose Humans are daily exposed to many environmental pollutants, some of which being suspected to be thyroid disruptors. Some populations could be particularly susceptible to thyroid disruption, such like diabetics due to the well-known relation between the thyroid function and the control of carbohydrate homeostasis by pancreas. Therefore, the aim of this study was to investigate the associations between the exposure to several persistent and non-persistent chemicals and thyroid hormones levels in children with type 1 diabetes.

Methods Blood and urine sample were collected from 54 children diagnosed for type 1 diabetes mellitus. The concentrations of 7 phthalate metabolites, 4 parabens, 7 bisphenols, benzophenone 3 and triclosan were measured in urine, while 15 organochlorine pesticides, 4 polychlorinated biphenyls (PCBs) and 7 perfluoroalkyl substances were analyzed in serum samples. In the same time, the blood levels of free thyroxine (fT4), thyroid stimulating hormone (TSH) and glycated hemoglobin (Hb1Ac) were determined.

Results We highlighted positive associations between serum perfluorohexane sulfonate and urinary monoethylphthalate levels, and TSH level in blood. We also found that PCB 138 was positively associated to fT4 while urinary levels of bisphenol F were negatively correlated to this hormone. Finally, we observed positive associations between Hb1Ac levels and the contamination by PCB 153 and two urinary phthalate metabolites: mono-2-ethyl-5-hydroxyhexyl phthalate and mono-2-ethyl-5-oxoxyhexyl phthalate.

Conclusion Our results showed that our small cohort of children with type 1 diabetes mellitus is potentially susceptible to thyroid disruptions by some pollutants. Moreover, for these children, both di-(2-ethylhexyl) phthalate metabolites would potentially hamper the glucose homeostasis. Nevertheless, additional studies are mandatory to further explore these findings.

Keywords Children · Endocrine disruptors · Thyroid hormones · Glycated hemoglobin · Type 1 diabetes

Abbreviations

fT4	Free thyroxine
BP	Bisphenol
TT4	Total thyroxine
4,4'-DDE	4,4'-Dichlorodiphenyldichloroethylene
PFNA	Perfluorononanoic acid
PFAS	Perfluoroalkyl substance
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
PCB	Polychlorobiphenyls
anti-TPO	Anti-thyroid peroxidase
anti-Tg	Anti-thyroglobulin
HbA1c	Glycated hemoglobin
HCH	Hexachlorohexane
HCB	Hexachlorobenzene
SPE	Solid phase extraction
GC	Gas chromatography
MS	Mass spectrometer
PFHxS	Perfluorohexane sulfonate
PFOS	Perfluorooctane sulfonate
PFHpA	Perfluoroheptanoic acid
PFOA	Perfluorooctanoic acid
PFDA	Perfluorodecanoic acid

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PFUdA	Perfluoroundecanoic acid
MEP	Monoethyl phthalate
MiBP	Mono-iso-butyl phthalate
MnBP	Mono-n-butyl phthalate
MBzP	Monobenzyl phthalate
MEHP	Mono-2-ethylhexyl phthalate
5-OH-MEHP	Mono-2-ethyl-5-hydroxyhexyl phthalate
5-oxo-MEHP	Mono-2-ethyl-5-oxohexyl phthalate
MeP	Methylparaben
EP	Ethylparaben
PrP	N-propylparaben
BP	N-butylparaben
BP3	Benzophenone-3
MRM	Multiple reaction monitoring
ECLIA	Electrochemiluminescence immunoassay
DF	Detection frequency

Introduction

The increasing incidence of thyroid disorders in the general population is suspected to be partly explained by the growing contamination of our environment and consequently the human organism by several chemicals able to disrupt the thyroid homeostasis (Boas et al. 2012). Several epidemiological studies showed correlations between exposition to some chemicals and the thyroid function in humans. For instance, recently, Zhang et al. 2021 showed associations between the urinary concentration of several phthalate metabolites and modification of the levels of free thyroxine (fT4) in patients with thyroid nodules. A positive association between bisphenol S (BPS) urinary levels and total thyroxine (TT4) concentrations measured during the first trimester of pregnancy was found in Dutch women (Derakhshan et al. 2021). In one of our previous works, we highlighted negative associations between contamination by 4,4'-dichlorodiphenyldi-chloroethylene (4,4'-DDE) and perfluorononanoic acid (PFNA, a perfluoroalkyl substance (PFAS)) measured in cord blood and TSH determined 3 days after birth in a cohort of male newborns (Dufour et al. 2018).

Moreover, Webster et al. 2014, reported that an increased PFASs concentration in the serum of pregnant women with high concentration of anti-thyroid peroxidase antibodies was associated with higher thyroid stimulating hormone (TSH) levels and lower fT4 concentration. They suggested that individuals whose the thyroid function is weakened by the presence of multiple stressors (e.g., anti-thyroid peroxidase antibodies, pregnancy or diabetes) are more vulnerable to the effects of thyroid disruptor compounds, and these findings would be explained by what they called a "multiple hit hypothesis".

On the other hand, the relation between the control of the glycemia by the endocrine pancreas and the thyroid function is well established. It has been demonstrated that hypothyroidism is associated with an increased resistance to insulin (Cettour-Rose et al. 2005; Maratou et al. 2009) while hyperthyroidism promotes the hepatic gluconeogenesis and the glucose output from the liver and thus hyperglycemia (Li et al. 2017; Mokuno et al. 1999). Some impacts of the diabetes on the thyroid function were also reported. For instance, diabetes was associated with a reduction of the nocturnal serum peak of TSH and the free triiodothyronine (T3) serum levels (Coiro et al. 1997). Moreover, insulin acts as a growth factor on thyroid tissue and higher concentrations of insulin are associated with a higher risk to develop thyroid nodules (Ayturk et al. 2009; Rezzonico et al. 2008). It is therefore not surprising to find that thyroid disorders are more prevalent in type 1 and type 2 diabetes patients than in healthy general population (Araujo et al. 2008; Jali et al. 2016; Perros et al. 1995; Spaans et al. 2017).

In children with type 1 diabetes, the thyroid function is therefore under additional stress due to the presence of the metabolic disease. Consequently, considering the multiple-hit hypothesis, we postulate that children with type 1 diabetes are more susceptible to thyroid disruptors.

Thenceforth, the objective of the present work was to explore the associations between the exposure to several suspected thyroid disruptors and thyroid hormones levels in children with type 1 diabetes. For this purpose, 15 organochlorine pesticides or metabolites, 4 polychlorobiphenyls (PCBs), and 7 PFASs were measured in serum samples, while 7 bisphenols (BPs) including among others BPA, BPS, BPF, triclosan, 7 phthalate metabolites, 4 parabens, and benzophenone 3 were quantified in urine samples collected from 54 diabetics children (type 1). In parallel, blood thyroxin and TSH concentrations were measured to assess the thyroid function. Moreover, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies were also determined in this cohort because of they are potentially additional thyroid stressors. In addition, we tested associations between glycated hemoglobin (HbA1c) a biomarker of diabetes control and pollutant contamination.

Materials and methods

Study population

Fifty-four children followed for type 1 diabetes at the Department of Pediatric Endocrinology of the University Hospital of Liege were recruited between March 2017 and April 2018 with parental consent. Blood samples were collected for medical follow-up of children and were analyzed during the day for thyroid hormones and HbA1c. In addition, a clot activator tube without gel was collected as well as a spot urine sample. After collection, these samples were

transferred to the laboratory of Toxicology of the University Hospital of Liege. Blood samples were centrifuged at 3000 rpm for 5 min to collect the serum fraction. Serum and urine samples were stored at − 20 °C until analysis. The protocol was approved by the Hospital Faculty Ethics Committee of the University of Liege (approval number: 2016–296).

Analytical procedures

Analysis of PCBs and organochlorine pesticides in serum

In the serum of patients, 15 pesticides or metabolites, (namely alpha-, beta-and gamma-hexachlorohexane (α-, β- and γ-HCH), hexachlorobenzene (HCB), aldrin, dieldrin, endrin, trans-chlordane, oxychlordane, trans-heptachlor ep-oxide, cis-and trans-nonachlor, 2,4′- and 4,4′-dichlorodiphenyldi-chloroethylene (4,4'-DDE), beta-endosulfan) and 4 PCBs (− 118, − 138, − 153 and − 180) were quantified according to the methodology described in Pirard et al. 2018 (Pirard et al. 2018). Briefly, acetonitrile and a saturated potassium carbonate solution were added to the sample to denaturize proteins. Chlorinated compounds were extracted from the denatured sample with a hexane–acetone mixture (9/1 v/v). The organic layer was transferred on a solid phase extraction (SPE) cartridge for further purification and then evaporated nearly to dryness with nonane as keeper. Then extract was analyzed using a gas chromatography (GC) coupled to a triple quadrupole mass spectrometer (MS) operating in negative chemical ionization mode.

Analysis of PFAS in serum

Perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), PFNA, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUdA)) were measured in serum as previously detailed (Dufour et al. 2018). In brief, after protein denaturation with a formic acid/water mixture (1/1, v/v), the sample was extracted on a weak anionic exchange SPE cartridge. The eluate was evaporated to dryness and reconstituted in a mixture of mobile phases. The quantification was performed using a liquid chromatography (LC) coupled to a triple quadrupole MS.

Analysis of phthalate metabolites, parabens and benzophenone-3 in urine

The urinary concentrations of 7 phthalate metabolites namely monoethyl phthalate (MEP), mono-iso-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (5-OH-MEHP) and mono-2-ethyl-5-oxohexyl phthalate (5-oxo-MEHP), of 4 parabens namely methylparaben (MeP), ethylparaben (EP), n-propylparaben (PrP) and n-butylparaben (BP), and benzophenone-3 (BP3) were determined according to the methodology developed Dewalque et al. 2014. Briefly, after an enzymatic hydrolysis performed overnight, sample was extracted on a SPE cartridge and injected on a LC–MS instrument operating in multiple reaction monitoring (MRM).

Analysis of triclosan and bisphenols in urine

The level of triclosan and 7 BPs (namely, -A, -AF, -F, -Z, -AP, -P and S) were measured in 3 mL of urine sample. Twenty µL of an internal standard solution (BPA-d_{14}, BPS-d_8 and triclosan-$^{13}C_{12}$ at 1 mg/L) were added to the sample and then a hydrolysis was performed with β-glucuronidase and sulfatase in sodium acetate buffer (1 M, pH = 4.5) at 40 °C during 30 min. Two hundred µL of formic acid were added to the mixture to end the reaction. The sample was sonicated during 15 min, centrifugated and then loaded on an Oasis HLB SPE cartridge (3cm^3, 60 mg, Waters) previously conditioned by 3 mL of dichloromethane, 2 × 3 mL of methanol and 3 mL of LC–MS grade water. The cartridge was washed with 3 ml of water (LC/MS grade), and centrifugated (5000 rpm during 5 min) to be completely dried. The elution of analytes was performed with 2 × 2.5 mL of a methanol/dichloromethane (1/1, v/v) mixture. The eluate was evaporated to dryness under a gentle stream of nitrogen at 30 °C and then reconstituted in 1 mL of water and 50 µL of KOH 2 M. This aqueous mixture was extracted with 3 mL of ethyl acetate. The organic layer was collected and evaporated to dryness under a gentle stream of nitrogen at 30 °C. The residue was derivatized by the addition of 30 µL of ethyl acetate and 20 µL of N-methyl-N-(trimethylsilyl)trifluoroacetamide and injected on an Agilent 7890A GC/7000A GC Triple Quad mass spectrometer (Agilent Technologies, California, USA) equipped with an Agilent HP-5MS capillary column (30 m × 0.25 mm i.d. × 0.25 µm internal film thickness). One microliter was injected in pulsed splitless mode (50 psi for 1.25 min) at 250 °C. The flow of carrier gas (Helium) was constant and set at 1.23 mL/min. The temperature gradient was set as follows: the initial temperature was 70 °C held for 1.25 min, then increase to 210 °C at the rate of 75 °C/min, then to 250 °C at the rate of 7 °C/min and finally to 325 °C at the rate of 20 °C/min, the final temperature was held for 3 min. The ionization was performed with an electronic impact source (electronic energy: − 70 eV, temperature: 230 °C). The temperatures of the transfer line and the quadrupoles were set at 250 °C and 150 °C respectively. Table 1 gathered MRM transitions, internal standard used and energy collision for each analyte.

Table 1 MRM transitions monitored, internal standard and energy collision used for the analysis of each analyte

Compounds	MRM transition (m/z)	Collision energy (eV)	Internal standard	LOQ (ng/mL)
BPAF	411→ 73	33	BPA-d_{14}	0.06
	480 → 411.1	**14**		
BPF	343.9 → 73	36	BPA-d_{14}	0.07
	343.9 → 179	**22**		
BPA-d_{14}	**368 → 73**	**39**		
	368 → 197	26		
BPA	356.9 → 73	39	BPA-d_{14}	0.29
	356.9 → 191.1	**21**		
BPZ	368.9 → 73	32	BPA-d_{14}	0.06
	368.9 → 203	**14**		
BPS-d_8	**401.7 → 73**	**39**		
	386.7 → 73	36		
BPS	394 → 73	39	BPS-d_8	0.09
	379 → 73	**34**		
BPAP	418.9 → 73	37	BPA-d_{14}	0.21
	433.9 → 419.2	**14**		
BPP	474.9 → 73	39	BPA-d_{14}	0.09
	474.9 → 207.1	**26**		
Triclosan-$^{13}C_{12}$	**371.7 → 206.1**	**20**		
	358.8 → 206.1	20		
Triclosan	**359 → 200**	**15**	Triclosan-$^{13}C_{12}$	0.20
	344.7 → 200	15		

MRM transitions used for the quantification are in bold

Thyroid hormones and anti-thyroid antibodies

Thyroxine and TSH concentrations were measured using electrochemiluminescence immunoassay (ECLIA) kit provided by Roche Diagnostics (Cobas 8000 Analyzer e602 module, Germany) following the manufacturer's instructions. Anti-TPO and anti-Tg antibodies were also determined using an ECLIA kit provided by Roche Diagnostics, cutoff values for abnormal levels were set at 34 IU/mL and 115 IU/mL respectively.

Glycated hemoglobin

HbA1c levels were determined on ion exchange HPLC HA-8180 from Menarini Diagnostics (Firenze, Italy). Photometer was used to identify (according to the retention time) and quantify the different hemoglobin fractions.

Statistical analysis

The statistical analyses were performed using Excel 2013 (Microsoft, Redmond, WA) and RStudio (version 3.4.1; R Project for Statistical Computing). Statistical significance was set at $p < 0.05$. Pollutant concentrations measured below the limit of quantification were set at LOQ × detection frequency (DF) (Ali et al. 2013; Dirtu et al. 2010). Because of left skewed distribution, natural logarithmic transformation was applied to the concentrations of pollutants, fT4, HbA1c and TSH + 1 (the constant 1 was added because some measurements of TSH were close to zero (Dufour et al. 2018)). Statistical analyses were solely performed with pollutants showing DF > 20%. When DF ranged from 20 to 70%, the contamination status (detected vs. non-detected) was used while pollutants with DF above 70% were treated as continuous variables. Two outlier measurements of TSH were excluded from the analyses. Generalized linear models were computed to assess the association between TSH, fT4 or HB1Ac on one hand and individual pollutants on the other hand. All statistical models were adjusted for age and gender. Furthermore, additional models for thyroid hormones were computed with the presence of anti-thyroid antibodies and overweight status (according to age, gender and BMI) and overweight status was added to the models assessing the relation between pollutant concentrations and HbA1c levels. For the computation of models assessing the association between urinary pollutant concentrations and biomarkers, urinary concentrations were corrected by creatinine level.

Results

Sociodemographic information about the study population are gathered in Table 2. Briefly, children were aged from 3 to 18 years with a median age of 14 years. Among them, 33 (61.1%) were boys and 21 (38.9%) were girls. Anti-thyroid antibodies were found in 8 (14.8%) children and 20 (37%) were overweight (according to age and gender specific reference values). Among the pollutants measured in urine and serum, 23 were positively quantified in more than 20% of the samples, i.e.: 3 PCBs, 5 PFASs, 7 phthalate metabolites, 3 parabens, 3 bisphenols, triclosan and BP3. Among organochlorine pesticides, only HCB, b-HCH and 4,4'-DDE were highlighted in few samples (in 9.3, 9.3 and 1.9% respectively) while all others were never detected. Detection frequencies (DF), mean, median and ranges concentrations are reported in Table 3. Adjusted regression coefficients and associated p-value computed for associations between each pollutant and the endocrine parameters are gathered in Table 4. Regarding the serum pollutants, we reported positive associations between PFHxS ($\beta = 0.159$, 95% confidence interval (95% CI): (0.016, 0.302)) and TSH, and between PCB 138 and fT4 ($\beta = 0.112$, 95% CI: (0.006, 0.219)) but these associations disappeared when adjusted for the presence of anti-thyroid antibodies and overweight status. We also found positive association between HbA1c and PCB 153 but solely when model was adjusted for overweight status ($\beta = 0.058$, 95% CI: (0.003, 0.114)). Concerning the urinary markers, we observed a positive association between MEP and TSH ($\beta = 0.213$, 95% CI: (0.071, 0.356)) while negative correlation between BPF ($\beta = -0.138$, 95% CI: (− 0.253, − 0.023)) and fT4 was observed. Finally, we showed positive associations between HbA1c and both 5-oxo-MEHP ($\beta = 0.070$, 95% CI: (0.001, 0.139)) and 5-OH-MEHP ($\beta = 0.070$, 95% CI: (0.004, 0.137)). In our models, we used natural log transformed values for the pollutant concentrations, therefore the β coefficient should be interpreted as the increase in biomarker level for each increase by a factor of 2.72 of the pollutant concentration.

Table 2 Sociodemographic information about the study population

	N	Mean	Median	Range	%
Age (years)	54	12.9	14	3–14	
Sex					
Girls	21				38.9
Boys	33				61.1
Overweight					
Yes	20				37.7
No	33				62.3
Anti-thyroid antibodies					
Yes	8				17.0
No	39				83.0
Maximal parental level of education					
Primary	1				1.9
Secondary	30				55.6
Short cycle higher education	12				22.2
Long cycle higher education	2				3.7
University	8				14.8
Post university	1				1.9

Discussion

The first objective of our study was to assess the associations between pollutants contamination and thyroid biomarkers. Our results highlight that increased serum levels of PFHxS and PCB 138 were associated with respectively increased levels of TSH and fT4 (however, these associations disappeared when the models were adjusted for obesity status and the presence of anti-thyroid antibodies), while higher levels of TSH and fT4 were observed for children showing respectively higher MEP levels and lower BPF levels in their urine. The second objective of the present work was to explore the correlations between pollutant exposure and the glucose homeostasis estimated by the measurement of the HB1Ac. We reported negative association with PCB 153 (but only when the model is adjusted by overweight status) and positive associations with 5-oxo-MEHP and 5-OH-MEHP.

In the present study, serum and urinary markers were considered separately because they do not represent the same time windows of exposure. Indeed, the pollutants measured in serum (e.g., PFASs and PCBs) belong to the family of persistent organic pollutants characterized by long half-life in the human body (several months or even years) and thus the levels measured are representative of a long-term exposure, or even a whole life exposure. The potential associations between persistent pollutants and endocrine biomarkers could thus be explained by long-term effects. On the other hand, the pollutants measured in urine (e.g., BPs, BP3, triclosan, parabens and phthalate metabolites) are rapidly eliminated from the organism (some hours), and urinary levels are thus representative of short term exposure. Therefore, putative correlation between urinary pollutants and endocrine biomarkers are more probably explained by short term mechanisms. For instance, BPA and some phthalates would be able to displace thyroid hormones from transthyretin (a serum protein involved in the thyroid hormone transport) (Ishihara et al. 2003) and could thus rapidly interfere with free thyroid hormones levels. Therefore, measuring both long and short term exposure markers should be relevant even if the underlying biological mechanism would likely differ.

Table 3 Detection frequencies (DF), median concentrations, mean concentrations and ranges measured in serum for PCB 138, PCB 153, PCB 180, hexachlorobenzene (HCB), beta-hexachlorohexane (b-HCH), 4,4′-dichlorodiphenyldichloroethylene (4,4'-DDE), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), and in urine for monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-iso-butyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (5-OH-MEHP) and mono-2-ethyl-5-oxohexyl phthalate (5-oxo-MEHP), methylparaben (MeP), ethylparaben (EP) and n-propylparaben (PrP), triclosan (TCS) and bisphenols (BP) -F, -A and -S

Compounds	DF (%)	Median (ng/mL)	Mean (ng/mL)	Range (ng/mL)
Serum				
PCB				
PCB 138	61.1%	0.38	0.40	<LOQ-1.22
PCB 153	55.6%	0.08	0.11	<LOQ-0.41
PCB 180	55.8%	0.06	0.07	<LOQ-0.27
OCP				
HCB	9.3%	<LOQ	<LOQ	<LOQ-0.11
b-HCH	9.3%	<LOQ	<LOQ	<LOQ-0.08
4,4'-DDE	1.9%	<LOQ	<LOQ	<LOQ-0.18
PFAS				
PFHxS	100.0%	0.42	0.71	0.15-12.8
PFOS	96.2%	1.51	1.77	<LOQ-5.66
PFOA	100.0%	1.08	1.35	0.30-4.76
PFNA	98.1%	0.36	0.44	<LOQ-1.51
PFDA	53.8%	0.16	0.19	<LOQ-0.88
Urine				
Phthalate metabolites				
MEP	100.0%	20.2	77.9	1.21-818
MnBP	100.0%	13.6	21.7	3.01-193
MiBP	97.9%	9.87	16.5	<LOQ-93.4
MBzP	81.3%	1.65	3.74	<LOQ-46.7
MEHP	65.2%	1.12	6.70	<LOQ-212
5-OH-MEHP	97.9%	5.72	13.5	<LOQ-303
5-oxo-MEHP	95.8%	4.32	9.34	<LOQ-187
Parabens				
MeP	37.0%	<LOQ	44.7	<LOQ-625
EP	25.6%	<LOQ	7.64	<LOQ-291
PrP	22.9%	<LOQ	2.63	<LOQ-26.8
Bisphenols				
BPF	69.8%	0.17	0.38	<LOQ-2.50
BPA	80.4%	1.16	3.07	<LOQ-53.8
BPS	65.1%	0.18	0.55	<LOQ-6.97
Miscellaneous				
BP3	61.0%	0.90	9.61	<LOQ-26.4
TCS	45.7%	<LOQ	1.33	<LOQ-26.3

PCB: polychlorobiphenyl, *OCP*: organochlorine pesticide, *PFAS*: perfluoroalkyl substance

In Tables 5, 6 are gathered the findings of other studies assessing the associations between some pollutant contaminations measured in serum and in urine respectively, and thyroid hormone levels in children and/or adolescents. If our results seemed to be not corroborated by any other studies, these tables also highlight the lack of consistency between all study results. According to the multiple-hit theory (Webster et al. 2014), our diabetic children population is suspected to be particularly vulnerable to pollutant actions on their weakened thyroid function compared to healthy children, therefore it was not entirely unexpected to observe some associations not previously reported for healthy populations. Only two other studies, but involving a very low number of individuals, explored the thyroid function regarding the pollutant exposure levels in children with thyroid function potentially hampered by other pathologies (Kim et al. 2016; Sur et al. 2019), but neither of them observed an association between phthalate or PFAS exposure levels and thyroid hormone levels. Several parameters may explain these apparent discrepancies between all studies gathered in Tables 5, 6. First, the levels of exposure may differ from one study to another. For instance, the median concentration measured in our population for PFOA was 1.08 ng/mL while the median level determined in the population of children recruited by Lopez-Espinosa et al. 2012 and living near a chemical plant was 29.3 ng/mL. Second, some racial

Table 4 Associations between TSH, fT4 and HB1AC and pollutant contaminations in multivariate linear regression models, significance level set at $p < 0.05$ (indicated in bold)

	Ln(TSH + 1)				Ln(fT4)				Ln(HB1AC)			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[c]	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Serum												
PCB 153 (Detected vs non-detected)	− 0.080	[− 0.277, 0.117]	− 0.110	[− 0.314, 0.094]	− 0.017	[− 0.125, 0.091]	− 0.004	[− 0.114, 0.104]	0.054	[− 0.000, 0.109]	**0.058**	**[0.003, 0.114]**
PCB 138 (Detected vs non-detected)	− 0.015	[− 0.224, 0.194]	0.025	[− 0.197, 0.247]	**0.112**	**[0.006, 0.219]**	0.092	[− 0.017, 0.202]	− 0.044	[− 0.100, 0.012]	− 0.050	[− 0.107, 0.007]
PCB 180 (Detected vs non-detected)	0.002	[− 0.201, 0.205]	− 0.037	[− 0.252, 0.177]	− 0.089	[− 0.195, 0.017]	− 0.086	[− 0.191, 0.019]	0.030	[− 0.027, 0.086]	0.032	[− 0.025, 0.090]
PFDA (Detected vs non-detected)	0.037	[− 0.162, 0.235]	0.072	[− 0.137, 0.282]	− 0.042	[− 0.143, 0.059]	− 0.042	[− 0.152, 0.068]	0.007	[− 0.050, 0.063]	0.002	[− 0.055, 0.060]
Serum												
Ln(PFHxS)	**0.159**	**[0.016, 0.302]**	0.145	[− 0.001, 0.293]	− 0.045	[− 0.124, 0.033]	− 0.039	[− 0.123, 0.044]	0.009	[− 0.035, 0.052]	0.011	[− 0.033, 0.055]
Ln(PFOA)	0.046	[− 0.127, 0.220]	0.046	[− 0.133, 0.227]	− 0.085	[− 0.174, 0.005]	− 0.083	[− 0.177, 0.010]	− 0.009	[− 0.060, 0.041]	− 0.009	[− 0.060, 0.042]
Ln(PFNA)	− 0.024	[− 0.185, 0.137]	− 0.018	[− 0.188, 0.151]	− 0.080	[− 0.164, 0.004]	− 0.086	[− 0.175, 0.001]	− 0.003	[− 0.050, 0.044]	− 0.006	[− 0.054, 0.042]
Ln(PFOS)	0.009	[− 0.179, 0.197]	0.011	[− 0.200, 0.224]	− 0.058	[− 0.159, 0.043]	− 0.068	[− 0.178, 0.040]	0.025	[− 0.028, 0.077]	0.020	[− 0.035, 0.074]
Urinary												
MeP (Detected vs non-detected)	− 0.111	[− 0.323, 0.101]	− 0.109	[− 0.334, 0.115]	− 0.036	[− 0.153, 0.081]	− 0.008	[− 0.127, 0.109]	0.004	[− 0.062, 0.069]	− .002	[− 0.069, 0.065]
EP (Detected vs non-detected)	− 0.092	[− 0.338, 0.155]	− 0.099	[− 0.368, 0.170]	− 0.115	[− 0.253, 0.023]	− 0.083	[− 0.223, 0.056]	0.007	[− 0.074, 0.088]	0.006	[− 0.076, 0.089]
PrP (Detected vs non-detected)	− 0.029	[− 0.306, 0.248]	− 0.062	[− 0.374, 0.249]	0.060	[− 0.111, 0.231]	0.037	[− 0.125, 0.199]	0.062	[− 0.023, 0.147]	0.062	[− 0.024, 0.148]
BP3 (Detected vs non-detected)	0.108	[− 0.106, 0.321]	0.081	[− 0.151, 0.315]	− 0.055	[− 0.179, 0.069]	− 0.044	[− 0.172, 0.083]	0.017	[− 0.051, 0.085]	0.025	[− 0.045, 0.096]
MEHP (Detected vs non-detected)	− 0.018	[− 0.235, 0.200]	− 0.019	[− 0.246, 0.207]	− 0.036	[− 0.152, 0.081]	− 0.025	[− 0.140, 0.090]	0.024	[− 0.043, 0.092]	0.028	[− 0.041, 0.097]
TCS (Detected vs non-detected)	− 0.085	[− 0.306, 0.137]	− 0.042	[− 0.293, 0.208]	0.040	[− 0.078, 0.159]	− 0.018	[− 0.143, 0.107]	− 0.003	[− 0.076, 0.070]	− 0.016	[− 0.095, 0.064]
BPF (Detected vs non-detected)	0.121	[− 0.104, 0.347]	0.177	[− 0.057, 0.411]	**− 0.138**	**[− 0.253, − 0.023]**	**− 0.131**	**[− 0.236, − 0.025]**	0.024	[− 0.053, 0.101]	0.026	[− 0.053, 0.105]
BPS (Detected vs non-detected)	0.004	[− 0.225, 0.232]	0.057	[− 0.188, 0.303]	− 0.053	[− 0.171, 0.064]	− 0.026	[− 0.146, 0.093]	0.071	[− 0.001, 0.143]	0.071	[− 0.007, 0.149]
Urinary (concentrations creat. corrected)												
Ln(MEP)	**0.213**	**[0.071, 0.356]**	**0.205**	**[0.055, 0.355]**	− 0.063	[− 0.149, 0.022]	− 0.070	[− 0.149, 0.008]	0.037	[− 0.015, 0.091]	0.037	[− 0.016, 0.092]

Table 4 (continued)

	Ln(TSH + 1)				Ln(fT4)				Ln(HB1AC)			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[c]	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Ln(MnBP)	− 0.139	[− 0.417, 0.138]	− 0.147	[− 0.446, 0.150]	− 0.045	[− 0.194, 0.103]	− 0.073	[− 0.215, 0.067]	0.045	[− 0.046, 0.137]	0.046	[− 0.047, 0.140]
Ln(MiBP)	− 0.001	[− 0.221, 0.218]	− 0.028	[− 0.258, 0.202]	− 0.067	[− 0.185, 0.050]	− 0.082	[− 0.192, 0.027]	0.037	[− 0.035, 0.111]	0.037	[− 0.036, 0.112]
Ln(5-oxo-MEHP)	− 0.152	[− 0.358, 0.053]	− 0.154	[− 0.373, 0.065]	− 0.053	[− 0.170, 0.062]	− 0.045	[− 0.156, 0.064]	**0.070**	**[0.001, 0.139]**	**0.071**	**[0.000, 0.141]**
Ln(5-OH-MEHP)	− 0.156	[− 0.355, 0.041]	− 0.163	[− 0.375, 0.049]	− 0.061	[− 0.175, 0.051]	− 0.056	[− 0.163, 0.050]	**0.070**	**[0.004, 0.137]**	**0.071**	**[0.003, 0.139]**
Ln(MBzP)	− 0.122	[− 0.318, 0.073]	− 0.200	[− 0.429, 0.028]	− 0.020	[− 0.141, 0.100]	− 0.052	[− 0.169, 0.065]	0.002	[− 0.064, 0.068]	0.002	[− 0.065, 0.069]
Ln(BPA)	0.039	[− 0.140, 0.220]	0.011	[− 0.178, 0.200]	− 0.031	[− 0.129, 0.066]	− 0.019	[− 0.113, 0.074]	0.016	[− 0.045, 0.078]	0.017	[− 0.045, 0.080]

[a]Adjusted for age and sex. [b]Adjusted for age, sex, overweighted status and presence of anti-thyroid antibodies. [c]Adjusted for age, sex and overweight status. *HCB* Hexachlorobenzene, *b-HCH* beta-hexachlorohexane, *4,4'-DDE* 4,4'-dichlorodiphenyldi-chloroethylene, *PFHxS* perfluorohexane sulfonate, *PFOS* perfluorooctane sulfonate, *PFOA* perfluorooctanoic acid, *PFNA* perfluorononanoic acid, and *PFDA* perfluorodecanoic acid, *MEP* monoethyl phthalate, *MnBP* mono-n-butyl phthalate, MiBP: mono-iso-butyl phthalate, *MBzP* monobenzyl phthalate, *MEHP* mono-2-ethylhexyl phthalate, *5-OH-MEHP* mono-2-ethyl-5-hydroxyhexyl phthalate, and mono-2-ethyl-5-oxohexyl phthalate, *MeP* methylparaben, *EP* ethylparaben, and *PrP* n-propylparaben, *TCS* triclosan, and *BP* bisphenols, -F, -A and -S

differences may also contribute to the inconsistency of the results. Indeed, the incidence of endocrine diseases (thyroid diseases included) was demonstrated to differ from a race to another (Golden et al. 2012), with some being more susceptible to endocrine disruption than others. Finally, to the best of our knowledge, no study assessed the mixture effect: each individual is daily exposed to hundreds of chemicals, and among them, several are potential thyroid disruptors and their effects may be additive or even synergic. Consequently, the study of pollutants considered individually may be an inappropriate way to explore the endocrine disruptor problematic. However, currently, several issues are associated to the study of mixture effect in epidemiological studies and the exploration of mixture effect in epidemiological studies is still in its infancy (Billionnet et al. 2012; Dufour et al. 2020).

Beside thyroid homeostasis disruption, it has been increasingly suggested that some environmental pollutants (i.e., organochlorines) may act as additional risk factor in the glucose homeostasis disruption although the involved biological mechanisms have not been yet fully established (Hectors et al. 2011). Indeed several studies have already assessed the association between pollutant internal contaminations and HbA1c levels, but results seemed inconsistent. For instance, in the present work, we found a positive association between PCB 153 and HbA1c while Arrebola et al. 2015 did not find any association with PCB 138, 153 or 180 in a cohort of Spanish women with history of gestational diabetes mellitus. Conversely, Esser et al. 2016 found significant positive correlations between several PCB congeners and HbA1c in a German cohort of formerly PCB-exposed workers. Although the associations between urinary concentration of pollutants (short term exposure markers) and HbA1c levels (representative of the mean glycemia during the previous four months) should be considered with caution, positive associations between HbA1c levels and two DEHP metabolites (i.e., 5-oxo-MEHP and 5-OH-MEHP) were highlighted, consistently with the observations of two other studies. Dales et al. 2018 who investigated the relations between phthalate exposure and several glucose homeostasis markers in a large population of Canadian people, found positive associations between the levels of HbA1c and MBzP, MiBP, 5-oxo-MEHP, MEHP and the sum of DEHP metabolites. Similarly, Duan et al. 2019 highlighted in a population of Chinese individuals a positive association between the urinary concentrations of 5-OH-MEHP and HbA1c levels. DEHP is a well-known activator of peroxisome proliferator-activated receptors (PPAR). These receptors have a key role in the glucose homeostasis (Stojanoska et al. 2017). Moreover, several investigations showed a glucose homeostasis disruption in rats experimentally exposed to DEHP (Boberg et al. 2008; Martinelli et al. 2006). Nevertheless, we cannot exclude that our findings

Table 5 Comparison of our findings with studies assessing the relations between pollutant contaminations measured in serum of children and thyroid hormone levels. *PFNA* perfluorononanoic acid, *PFOA* perfluorooctanoic acid *PFHxS* perfluorohexane sulfonate, *dl-PCBs* dioxin like PCBs, marker *PCBs* PCB 138, 153 and 180; ↑ = Positive association; ↓ = Negative association

Study	Population	Associations with	
		TSH	fT4
Perfluoroalkyl substances			
Caron-Beaudoin et al. 2019 (Caron-Beaudoin et al. 2019)	Children (3–19 years), First Nation children, Canada, $n = 198$	None	PFNA ↑
Kim et al. 2016 (Kim et al. 2016)	Infants with ($n = 27$) or without ($n = 13$) congenital hypothyroidism, South Korea	None	None
Lopez-Espinosa et al. 2012 (Lopez-Espinosa et al. 2012)	Children (1–17 years) living in proximity of chemicals facility, USA ($n = 10{,}725$)	PFOA ↓ (girls 1–5 years); PFNA ↑ (boys > 10 years)	Not assessed
Present study	Children (3–18 years) with diabetes 1 diagnosed, $n = 54$	PFHxS ↑	None
Alvarez-Pedrerol et al. 2008 (Alvarez-Pedrerol et al. 2008)	Children (4 years), general population, Menorca (Spain), $n = 259$	None	PCB 118 ↓
Croes et al. 2014 (Croes et al. 2014)	Adolescents (14–15 years), general population, Belgium, $n = 200$	None	∑dl-PCBs ↑ ∑marker PCBs ↑
Han et al. 2011 (Han et al. 2011)	Children (6–8 years), E-waste recycling area, China, $n = 369$	∑PCBs (18 congeners) ↑	Not assessed
Leijs et al. 2012 (Leijs et al. 2012)	Adolescents (14–18 years), general population, the Netherlands, $n = 33$	None	None
Schell et al. 2004 (Schell et al. 2004)	Adolescents (10–16.9 years), First Nation adolescents, Canada and USA, $n = 115$	∑PCBs (8 congeners) ↑	∑PCBs (8 congeners) ↓
Schell et al. 2008 (Schell et al. 2008)	Adolescents (10–16.9 years), First Nation adolescents, Canada and USA, $n = 252$	∑PCBs (8 congeners) ↑	∑PCBs (8 congeners) ↓
Xu et al. 2014 (Xu et al. 2014)	Children (8 years), E-waste recycling area ($n = 21$) and remove location ($n = 24$), China, = 369	None	None
Present study	Children (3–18 years) with diabetes 1 diagnosed, $n = 54$	None	PCB 138 ↑

are due to lifestyle or diet habits simultaneously associated with high exposure to phthalates and higher risk to present glucose homeostasis disruption. Large scale longitudinal studies are thus required to explore the mechanism linking DEHP and DEHP metabolites and HbA1c. On the other hand, no association between HbA1c levels and BPs was observed, while Tai and Chen 2016 and Silver et al. 2011 found positive association between BPA and HbA1c levels in Canadian adult males and American individuals.

The results reported in the present work should be considered with caution because of some limitations. First, the number of individuals included in our population is low which reduces the statistical power of the analysis. A larger cohort would allow the stratification of the statistical analyses by gender or age category, and the adjustment for additional cofounders such as food habits or physical activity. Furthermore, due to the lack of statistical power, we were unable to use statistical methods suited to exploring mixture effects such as Weighted Quantile Sum regression (Czarnota et al. 2015) or Bayesian Kernel Machine Regression (Bobb et al. 2015). Second, given the exploratory nature of our investigations, we did not apply any correction on p-value. Nevertheless, in regards of the number of covariates computed in the statistical models, we cannot exclude that some of our findings are due to chance. The transversal character of our study is a third limitation, indeed, we cannot exclude an inverse causation. For instance, the thyroid function is linked to many metabolic processes, which could potentially have an impact on the pollutant concentrations rather than the opposite. Finally several studies indicated that the concentrations determined in spot urine samples are moderate to poor predictors of exposure to non-persistent pollutants (Casas et al. 2018; Dewalque et al. 2014; Morgan et al. 2018), therefore questioning the representativeness of the levels measured and the associations highlighted especially with HbA1c which is a long-term marker of glycemia. Increase the number of urine samples collected per individual or increase the size of the population studied could

Table 6 Comparison of our findings with studies assessing the relations between pollutant contaminations measured in urine of children and thyroid hormone levels. *MMP* monomethylphtalate, *DBP* dibutylphthalate, *PA* phthalic acid, *DHEP* di(2-ethylhexyl) phthalate, *MECPP* mono(2-ethyl-5-carboxypentyl) phthalate, *MCPP* mono(3-carboxypropyl) phthalate, ↑ = positive association, ↓ negative association

Study	Population	Associations wi	
		TSH	fT4
Bisphenols			
Meeker and Ferguson 2011 (Meeker and Ferguson 2011)	Adolescents (12–19 years), general population, USA, $n=329$	None	None
Sur et al. 2019 (Sur et al. 2019)	Children (8–16 years), children with Hashimoto thyroiditis, Turkey, $n=29$	None	BPA ↓
Present study	Children (3–18 years) with diabetes 1 diagnosed, $n=54$	None	BPF ↓
Parabens			
Koeppe et al. 2013 (Koeppe et al. 2013)	Adolescents (12–19 years), general population, USA, $n=352$	None	None
Present study		None	None
Triclosan			
Koeppe et al. 2013 (Koeppe et al. 2013)	Adolescents (12–19 years), general population, USA, $n=352$	None	None
Braun et al. 2018 (Braun et al. 2018)	Children (3 years), general population, USA, $n=153$	None	TCS (mean of repeated measures) ↑
Present study	Children (3–18 years) with diabetes 1 diagnosed, $n=54$	None	None
Phthalates			
Huang et al. 2017 (Huang et al. 2017)	Children (2–9 years), general population, Taiwan, $n=337$	None	MEHP ↓ (girls)
Huang et al. 2020 (Huang et al. 2020)	Children (2–14 years), potential victims of phthalates tainted foods, Taiwan, $n=166$	MMP ↓; MBzP ↑	MMP ↓; MEP ↓
Kim et al. 2018 (Kim et al. 2018)	Children (0–19 years), general population, South Korea, $n=302$	PA ↑ (girls < 11 years); DEHP ↓ (girls ≥ 11 years)	MnBP ↓ (boys < 12 years); DBP ↓ (girls < 11 years); PA ↑ (girls < 11 years)
Kim et al. 2020 (Kim et al. 2020)	Children (6 years), general population, South Korea, $n=492$	None	MnBP ↓ (girls)
Meeker and Ferguson 2011 (Meeker and Ferguson 2011)	Adolescents (12–19 years), general population, USA, $n=329$	5-oxo-MEHP ↑; 5-OH-MEHP ↑; MECPP ↑	MCPP ↓
Morgenstern et al. 2017 (Morgenstern et al. 2017)	Children (3 years), general population, USA, $n=229$	None	5-OH-MEHP ↓ (girls); MnBP ↓ (girls); MiBP ↓ (girls); MEP ↓ (girls); 5-oxo-MEHP ↓ (girls)
Sur et al. 2019 (Sur et al. 2019)	Children (8–16 years), children with Hashimoto thyroiditis, Turkey, $n=29$	none	none
Tsai et al. 2016 (Tsai et al. 2016)	Children (< 18 years), potential victims of phthalates tainted foods, Taiwan, $n=250$	MnBP ↑; MBzP ↑	MnBP ↑; MiBP ↑
Weng et al., 2016 (Weng et al. 2017)	Chidlren (9–10 years), general population, Taiwan, $n=189$	MnBP ↑ (girls)	MiBP ↑ (girls); MEHP ↑ (girls); 5-oxo-MEHP ↑ (girls)
Wu et al. 2017 (Wu et al. 2017)	Children (5–7 years), region with numerous electronic manufacturing facilities, China, $n=216$	None	MEP ↑; MnBP ↑
Present study		MEP ↑	None

help although it was demonstrated to not perfectly compensate the high intra-individual variability (Frederiksen et al. 2013; Philippat and Calafat 2021). Instead of increasing the number of urine spots, alternative matrices can be considered to more accurately measure long-term exposure to non-persistent pollutants, such as hair (Claessens et al. 2022) or silicone wristbands (Samon et al. 2022) but these matrices also have their limitations.

Conclusion

This work investigated the link between the exposure to some environmental pollutants, from Persistent Organic Pollutants to some non-persistent plasticizers and antimicrobials, and thyroid disorders in type 1 diabetes children. Associations between the levels (in serum or urine) of some PFASs, PCBs, phthalates and bisphenols and thyroid hormone levels were highlighted, suggesting an impact of these pollutants on the thyroid function in this population suspected to be particularly vulnerable toward endocrine disruption. These findings should be confirmed by larger scale studies. Moreover, we found positive associations between HbA1c and di-2-ethylhexylphthalate metabolites consistently with previous observations on Chinese and Canadian cohorts. These findings should be explored more in depth by large scale longitudinal epidemiological studies and mechanistic investigation should be performed in laboratory to examine physiological processes associating these compounds and glycemia.

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Data availability Data will be made available on reasonable request.

Declarations

Conflict of interest Authors have no competing interests to declare.

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