Science of the Total Environment 770 (2021) 145262

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Multiple persistent organic pollutants in mothers' breastmilk: Implications for infant dietary exposure and maternal thyroid hormone homeostasis in Uganda, East Africa

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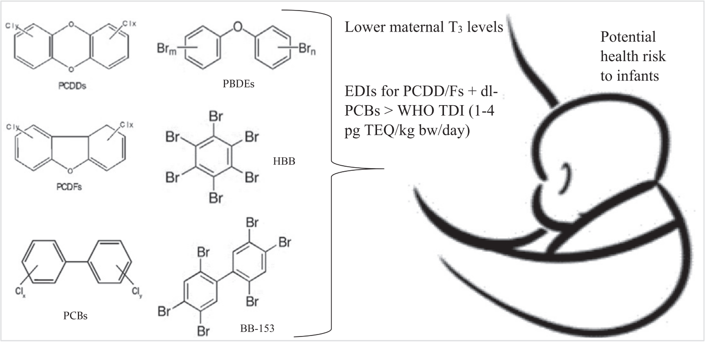
HIGHLIGHTS

- Dioxins were analysed in individual breastmilk samples for the first time in Uganda.
- Levels of BFRs, PCBs and PCDD/Fs in Uganda were amongst the lowest reported globally.
- Total WHO TEQ_{2005} for PCDD/Fs and dl-PCBs were 0.07–7.84 pg TEQ/g lw, respectively.
- PCB-169 and PCB-126 were associated with lower levels of T_3 in univariate models.
- Infant EDIs for dioxins exceeded WHO tolerable doses in majority samples.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 23 September 2020
Received in revised form 9 January 2021
Accepted 14 January 2021
Available online 20 January 2021

Editor: Adrian Covaci

ABSTRACT

Persistent organic pollutants (POPs) are ubiquitous contaminants with adverse health effects in the ecosystem. One of such effects is endocrine disruption in humans and wildlife even at background exposure concentrations. This study assessed maternal breastmilk concentrations of POPs; brominated flame retardants (BFRs), polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-*p*-dioxins/furans (PCDD/Fs), and the potential health risks posed to the nursing infants. We also evaluated the association of these POPs with total 3,3′,5-triiodo-L-thyronine (T_3), L-thyroxine (T_4), and 3,3′,5′-triiodo-L-thyronine (rT_3) levels measured in human breast milk. Thirty breastmilk samples were collected from Kampala, Uganda between August and December 2018.

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https://doi.org/10.1016/j.scitotenv.2021.145262

Keywords:
Persistent organic pollutants
Breastmilk
Dietary exposure
Thyroid hormones
Africa

Hexabromobenzene was not detected while the maximum level of 2,2′,4,4′,5,5′-hexabrombiphenyl was 64.7 pg/g lw. The median levels of total indicator PCBs, PBDEs, dioxin-like PCBs, and PCDD/Fs in the samples were 159 pg/g lw, 511 pg/g lw, 1.16 pg TEQ/g lw, and 0.4 pg TEQ/g lw, respectively. These levels were lower than those reported in other countries. Owing to their bio accumulative nature, PCBs −81, −169, and $\sum$PCDD/Fs increased with increase in maternal age. Estimated dietary intakes for dioxin-like PCBs and PCDD/Fs were lower than those reported elsewhere but were higher than the WHO tolerable daily intakes suggesting potential health risks to nursing infants. In adjusted single pollutant models, PCB-126, PCB-169, and $\sum PCB_{TEQ}$ were negatively associated with T_3, while 1,2,3,4,5,7,8-HpCDF was positively associated with rT_3. Although these associations did not persist in multipollutant models, our findings suggest potential thyroid hormone disruption by POPs in mothers. This may reduce the levels of thyroid hormones transferred from the mother to the neonates and, hence, adversely influence infant growth. A temporal study with a bigger sample size is required to corroborate these findings.

1. Introduction

Persistent organic pollutants (POPs) which include polychlorinated dibenzo-*p*-dioxins/furans (PCDD/Fs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), hexabromobenzene (HBB) and 2,2′,4,4′,5,5′-Hexabrombiphenyl (BB-153) are ubiquitous contaminants of anthropogenic origin with adverse effects in the ecosystem. PCDD/Fs are unintentional products of industrial and combustion processes, while PCBs have historical production and use in transformer and hydraulic fluids, and as additives in paints and oils (Degrendele et al., 2020). Brominated compounds, such as PBDEs and BB-153, are used as flame-retardants in polyurethane foam, furniture, mattresses and textiles (Chen et al., 2018; Liu et al., 2016). POPs are of global concern due to their persistence, long-range transport, potential for bioaccumulation in fatty matrices and toxicity (Bao et al., 2020; Hernández et al., 2020). As such, use of these chemicals has met restrictions from the Stockholm convention to which Uganda acceded in May 2004.

Many areas in Africa are experiencing rapid economic development (industrialization, population growth and urbanization). These developments, coupled with importation of e-waste and other consumer products from the developed world and improper waste management practices have led to increased human exposure to many organohalogen pollutants (Matovu et al., 2019; Matovu et al., 2020; Ssebugere et al., 2020). Human exposure to these compounds occurs through inhalation of dust, ingestion of contaminated foods, especially those of animal origin (Polder et al., 2016; Wu et al., 2018), and through geophagy (Müller et al., 2016). On the other hand, consumption of contaminated breast milk presents a major exposure pathway for nursing infants (Hernández et al., 2020). Infants are especially susceptible to the deleterious effects resulting from this exposure because their metabolic systems are still under development and they undergo rapid neurodevelopmental changes (Hernández et al., 2020).

Some of the well documented effects of PCDD/Fs, PCBs and PBDEs in humans include neurodevelopmental deficits, immune and hormonal toxicity, and cancer (Eskenazi et al., 2018; Guo et al., 2018; Hui et al., 2016; Nakajima et al., 2017). PCDD/Fs, PCBs and PBDEs resemble thyroid hormones (THs) in chemical structures (Lignell et al., 2016), and have been shown to regulate levels of THs by disrupting TH homeostasis in humans even at background levels (Berg et al., 2017; Li et al., 2020; Lignell et al., 2016). However, despite the health concerns surrounding persistent organic pollutants, there are still large data gaps regarding the levels of POPs in human samples in East Africa, and Africa at large (Ssebugere et al., 2019). For instance, only one study has reported on the occurrence of dioxins in individual human breastmilk samples in East Africa (Müller et al., 2019). This underscores the need for continuous biomonitoring of POPs in less studied regions in Africa.

The present study is part of a broader project investigating the levels of human body burdens of POPs in the region. Our pilot study on fifty breastmilk samples collected from occupationally-exposed primiparous mothers in Uganda revealed the occurrence of PBDEs in the samples (Matovu et al., 2019). In a bid to corroborate the findings, in the present study we recruited a second cohort of 30 (primiparous and multiparous) mothers and expanded the range of pollutants under investigation to include dioxins, polychlorinated biphenyls and alternative brominated flame retardants (BFRs). We also aimed at evaluating the potential effect of these POPs on maternal TH homeostasis by investigating the associations of these POPs in breastmilk with milk TH levels. Since there is a significant positive correlation between THs in milk and those in serum (Zhang et al., 2013), TH levels in milk may represent the levels of circulating THs in mothers. It should be noted that, although several studies have investigated the effect of POPs on TH homeostasis, most studies evaluate associations between breastmilk levels of POPs and TH levels in serum (Darnerud et al., 2010; Lignell et al., 2016). Only one study (Li et al., 2020) reported these associations between POPs and THs, both measured in breastmilk. This underscores the need for more studies on human milk to support the findings, especially given the likely regional differences in levels of maternal POP exposure, and the different dietary habits which could influence the TH levels. Besides, the study by Li et al. (2020) used mature milk samples. Therefore, there is need to investigate if the associations between POPs and TH levels exist in colostrum samples since colostrum is the sole dietary source for neonates and these first few days are a critical window in the development of the infants.

2. Materials and methods

2.1. Ethical considerations and study population

The study protocol was reviewed and approved by the Ethics and Research Committees of the National Council for Science and Technology (approval number HS 2263), and St. Francis Hospital Nsambya, Uganda. Prior to participation, the aim of the study was clearly explained to the mothers who signed an informed consent form. All information provided by the volunteers was kept confidential.

The participants in this study were identified during their routine antenatal visits to St. Francis Hospital Nsambya, Uganda. Recruitment into the study was based on the participants' willingness to participate, exposure history and their period of residence in Kampala, a developing city in Uganda, East Africa (Fig. S1). The city covers an area of 189 sq. kms, and is 23% urbanized, 60% semi-urbanized and 17% rural. As of 2019, the city was home to approximately 1.75 million residents from a wide range of tribal backgrounds and lifestyles. For instance, approximately 100,000 residents in the city were refugees from neighbouring countries such as Congo, Somalia, Rwanda, Eretria, Burundi, South Sudan, Rwanda and Ethiopia (KCCA, 2019). The diversity of the population in Kampala is representative of the general population in rapidly-developing areas in sub-Saharan Africa. The city therefore presented a suitable case for studying maternal burdens of POPs and their effects in the region.

Only healthy volunteers who had lived in Kampala for the last five years were requested to participate in the study. The participants should have no history of known occupational exposure to POPs. This was to generate a sample with only background exposure to POPs. Information about maternal age, pre-pregnancy weight, dietary habits during pregnancy, occupation and lifestyle at the time of sample collection were collected by filling a questionnaire modified from WHO guidelines (WHO, 2007).

2.2. Sample collection and target analytes

Between August and December 2018, thirty (30) maternal breastmilk samples (at least 20 mL each) were collected by manual expression directly into solvent-cleaned polypropylene bottles. The bottles were labeled with permanent stickers and packed in boxes containing dry ice, and then transported to the German Research Centre for Environmental Health, Munich, Germany. In the laboratory, the samples were kept at −20 °C prior to analysis of 17 PCDD/Fs congeners, four non-*ortho* PCBs, eight mono-*ortho*, six *indicator* PCBs, thirty-seven PBDE congeners, HBB, BB-153, and 3 THs.

All samples were collected between 2 and 9 days of postpartum. This time of breast milk sampling in our study is in contrast with the recommendation of at least two weeks by WHO (WHO, 2007). In this study, the recommended sampling time was not possible because in developing countries such as Uganda, reaching the mothers after they have left the hospitals is very hard. Moreover, a study by Yu et al. (2007) showed that no significant differences existed between the levels of persistent organic pollutants in colostrum and mature milk. Furthermore, although the amount of iodine in mothers' milk tends to increase during lactation, the levels of circulating THs do not change significantly in the first few months of lactation (Ilcol et al., 2006) and there is no significant difference between TH levels in colostrum and those in mature milk (Jansson et al., 1983). Hence comparisons between POPs and TH levels in this study and other studies might be valid.

2.3. Analytical procedures

2.3.1. Extraction, clean-up and analysis of samples for POP quantification

The samples were allowed to thaw at room temperature and were then extracted according to a method described by Li et al. (2020) with minor modifications. A milk sample (10 mL) was measured into a separating funnel and spiked with a mixture of sixteen $^{13}C_{12}$-labeled PCDD/Fs, sixteen $^{13}C_{12}$-labeled brominated flame retardants (BFR), twelve $^{13}C_{12}$-labeled dioxin-like (dl-) PCBs and six $^{13}C_{12}$-labeled indicator PCBs (*i*PCBs) congeners. The amount of each spiked congener was 0.2 to 0.4 ng for PCDD/Fs, 0.3 to 3 ng for BFR and 0.4 ng for all analysed PCBs. Deionized water was added to the sample to make up a total volume of 100 mL, followed by 8 mL of saturated potassium oxalate solution (saturated at 60 °C). 80 mL of ethanol, 40 mL of diethyl ether and 60 mL of *n*-pentane were added in succession; with thorough shaking of the mixture after addition of each solvent. When the distinct layers had separated, the upper (organic) phase was isolated. The remaining aqueous layer was further extracted twice more by shaking it with 60 mL of *n*-pentane each time. The organic extracts were combined, washed with 100 mL of deionized water, and dried using anhydrous sodium sulfate. The dried extract was concentrated to 2 mL using a rotary evaporator and further evaporated to dryness using a gentle stream of nitrogen gas for gravimetric determination of the lipid content. After lipid content determination, the lipid was dissolved in 2 mL of *n*-hexane and kept for lipid removal and clean-up which were performed on a DEXTech™ semi-automated sample preparation system (LCTech GmbH, Dorfen, Germany). The DEXTech methods used have been described elsewhere (Bernsmann et al., 2014; Bernsmann et al., 2013). Two fractions; one containing PCDD/Fs and *non-ortho* PCBs, and the other containing the *mono-ortho* PCBs, indicator PCBs and brominated compounds were collected. The fractions were concentrated to 10 μL before addition of recovery standards ($^{13}C_{12}$-labeled: 1,2,3,4-TCDD, 0.1,2,3,7,8,9-HxCDD, BDE-138, PCB-70, PCB-111, PCB-170).

Quantification of the target analytes was achieved using an Agilent gas chromatograph (HRGC) coupled with a Thermo high resolution mass spectrometer (HRMS) by isotope dilution method. Instrumental and chromatographic parameters are listed in Table S5.

2.3.2. Determination of thyroid hormone levels

Levels of 3, 3′, 5-triiodo-$_L$-thyronine (T_3), 3, 3′, 5′-triiodo-L-thyronine (rT_3) and L-thyronine (T_4) in breast milk were analysed using isotope-dilution liquid chromatography tandem mass spectrometry (LC-MS/MS). The measurement was performed with an Agilent 6470 triple quadrupole tandem mass spectrometry system coupled with Agilent 1290 Infinity II LC system. The method of analysis was previously described elsewhere (Li et al., 2018), with modifications further described by (Li et al., 2020). The method detection and quantitation limits were 0.01–0.13 and 0.10–0.42 pg/μL, respectively. Matrix effects ranged from −9.67 to 14.7%. Recoveries for THs in spiked samples ranged from 98 to 120%. Moreover, the intraday and interday variations were 0.47–6.91 and 1.37–7.71%, respectively.

2.4. Quality assurance/quality control

Quality assurance/Quality control procedures included procedural and spiked blank samples. For every set of five samples, we analysed a procedural blank to check for background contamination. In addition, each sample was spiked with ^{13}C-labeled standards. The recoveries of the standards ranged between 50 and 140%. Hence, the results comply with the requirements of Regulation (EU) no. 589/2014, and the levels were not corrected for recoveries.

The generated data were blank-corrected in the way that an average of all procedural blank values was subtracted from the sample values. Analytes whose concentrations after blank correction were lower than three times the standard deviation of the blank values were considered as not detectable (n.d.). Analytes in samples that were not detected before blank correction were also given as not detectable (n.d.). The limit of quantification (LOQ) of the instrumental methodology was considered as a signal/noise ratio of 9:1. LOQs varied from 0.005 to 0.06 pg/g lipid weight (lw) for PCDFs, 0.01–20.5 pg/g lw for PCDDs, 10–1700 pg/g lw and 0.03 to 500 pg/g lw for dl-PCBs, and 0.02–610 pg/g lw for brominated flame retardants (BFRs).

2.5. Statistical analysis

Statistical analyses were performed using SPSS statistic software, version 21 (IBM SPSS Inc., Chicago, IL, USA). Sums were only calculated for positive quantifiable samples, while median was reported only for those pollutants with a detection frequency of ≥50%. The other analytes were reported with ranges only. The 2005 WHO Toxic equivalence quotients (TEQs) for PCDD/Fs and dl-PCBs (Van den Berg et al., 2006) were used to calculate total TEQs. Normality of the lipid-normalized POP concentrations and THs was initially assessed using the Shapiro-Wilk tests. The levels were skewed and, hence, were $\log_{10}$-transformed to satisfy conditions of normality before further statistical analyses. Spearman's rank-order correlation coefficients (ρ) were calculated to evaluate bivariate associations between maternal demographic factors and the pollutant levels, as well as those amongst the different pollutants.

Single-pollutant models were established to investigate the associations between THs and each POP congener, while multipollutant models were conducted to evaluate associations between the levels of combinations of POPs and THs amongst the study population. TH levels were treated as dependent variables and POPs levels as independent variables of regression models. Only organohalogen pollutants with detection frequencies ≥70% were included in statistical models, while non-detects were replaced with values equal to half the corresponding LODs. Since congeners of each class of POPs have common adverse effects patterns, evaluating the effects of individual congeners and excluding congeners of low detection frequencies may underestimate the toxic potency of the combined exposure. Therefore, by assuming a dose addition principle, we also included sums of congeners in the statistical analyses to assess the combination effect of the congeners in each class of POPs (Müller et al., 2016). We assessed multicollinearity amongst predictor variables using pairwise correlation coefficients and variance inflation factors. In order to minimize multicollinearity and the number of independent variables (POPs) to be included in multivariate linear regression models, we conducted hierarchical cluster analysis of POPs based on correlations. Each cluster was then represented by POP closest in terms of Euclidean distance to the multidimensional cluster centre (Dormann et al., 2013).

We investigated associations between the potential covariates (maternal age, pre-pregnancy BMI, smoking status, and education level) and levels of POPs in bivariate models (Spearman's rank correlation analysis). Due to the small sample size, we combined results from all the samples and did not include parity amongst the potential covariates. Covariates associated with any of the maternal outcomes ($p \leq 0.05$) were included in the final models. The linearity fit of the regression models was checked by plotting the residuals around the fitted line and the robustness of the results was evaluated by sensitivity analysis where outliers with a standardized residual ≥3 were excluded from the regression models. In addition, we repeated the statistical analyses using levels of POPs in units of pg/mL milk, while controlling for percent lipid content.

3. Results and discussion

3.1. Maternal and infant characteristics

The characteristics of the sample population are shown in Table 1. All participants were aged between 17 and 38 years (average age 29.1 years) with an average pre-pregnancy body mass index (BMI) of 29.4 (range; 22.4–41.8). Twenty-one (70%) of the participants were first-time mothers, and 80% of them had attained at least secondary school level education. None of the participants was an active or retired smoker. Regarding infant characteristics, the median birth weight was 3.25 kg and 47% of the infants were females. Maternal age was negatively associated with infant birth weight (Spearman's rho, $\rho = -0.430$, $p = 0.018$). No significant association was observed between pre-pregnancy BMI and maternal age ($\rho = -0.078$, $p = 0.683$) or infant birth weight ($\rho = 0.241$, $p = 0.199$).

Table 1
Demographic and sample characteristics of the participants and levels of THs ($N = 30$).

Maternal/infant characteristic	Mean ± SD	Median	Minimum	Maximum
Maternal age (years)	29.1 ± 4.73	29	17	38
Pre-pregnancy BMI (kg/m^2)	29.4 ± 5.11	27.8	22.4	41.8
Infant birthweight (kg)	3.19 ± 0.69	3.25	2.3	4.2

		Frequency (person, %)
Parity	*Primiparous*	21 (70)
	multiparous	9 (30)
Infant sex	*Male*	14 (47)
	Female	16 (53)
Maternal educational level	*Primary school level*	6 (20)
	Secondary school level	16 (53)
	University level	8 (27)
Smoking habits	Active/retired	0
	Never	30 (100)

Sample characteristic	Mean ± SD	Median	Minimum	Maximum
Lipid content (%)	6.52 ± 2.47	6.3	1.41	12.5
Thyroid hormones				
T3 (pg/μL)	0.507 ± 0.164	0.463	0.173	0.894
rT3 (pg/μL)	0.014 ± 0.004	0.013	0.004	0.04
T4 (pg/μL)	0.635 ± 0.248	0.541	0.359	1.31

SD = standard deviation.

Lipid content in the breast milk samples ranged from 1.41 to 12.5% (median; 6.30%). Levels of T_3, rT_3 and T_4 were 0.173–0.894 (mean; 0.507), 0.0038–0.401 (0.014) and 0.359–1.309 (0.541) pg/μL, respectively. The levels of THs in breastmilk samples observed in this study were comparable to those reported in mature breastmilk samples in Germany (0.57 ± 0.20, 0.02 ± 0.01, and 0.13 ± 0.03 pg/μL, respectively) (Li et al., 2020). The levels of T_3 and T_4 in our study were lower than those reported in preterm breastmilk samples in The Netherlands (0.86 ± 0.38 pg/μL and 0.14 (0.08–0.18) μg/mL for T_3 and T_4, respectively) (Van Wassenaer et al., 2002). Associations between T_3 and both rT_3 ($\rho = 0.076$, $p = 0.690$) and T_4 ($\rho = -0.060$, $p = 0.755$) were not significant, while that between rT_3 and T_4 was positive and significant ($\rho = 0.421$, $p = 0.020$).

3.2. Levels of BFRs

The levels of BFRs detected in the samples are presented in Table 2. Amongst these, HBB was not detected in any of the samples, consistent with a recent study in Northern Tanzania (Müller et al., 2016) which found non-detectable levels of HBB in maternal breast milk samples. BB-153 was detected in only 16.7% of the samples with a maximum concentration of 64.7 pg/g lw. BB-153 levels in our study are lower than those reported in breastmilk samples from developed countries such as the UK (range; 60–790 pg/g and median; 80 pg/g lw) (Bramwell et al., 2014), Belgium (range; <100–500 pg/g lw) (Aerts et al., 2019), Ireland (mean; 130 pg/g lw) (Pratt et al., 2013), Denmark (range; 41–1499; mean; 200 pg/g lw) and Finland (26–1204; 134 pg/g lw) (Shen et al., 2007). The results suggest differences in production and use of products containing the pollutants, and a higher exposure for mothers in developed countries compared to those in Uganda. BB-153 has had historical use as part of a commercially available flame retardant mixture of HBBs which is added to thermoplastics used in housings for office equipment and it comprises about 60% of this mixture (Hardy, 2002; Wang et al., 2019).

Twenty-nine (29) out of 37 BDE congeners were detected in the milk samples. Total ($\sum$) PBDEs ranged from <0.1 to 8861 pg/g lw with a median value of 511 pg/g lw. BDE-47 (range; <89.5–3661 pg/g lw and median; 392 pg/g lw) was the most dominant congener and this contributed 48.8% of $\sum$PBDEs on average. This was followed by BDE-66 (<5.8–125 pg/g lw; median 14.4 pg/g lw) and BDE-49 (range; <4.7–88.5 and median; 14.4 pg/g lw). BDE-209 was the major congener (contributed 52.1% to $\sum$PBDEs) in each of the 26.7% samples in which it was detected. The maximum concentration of 4763 pg/g lw of BDE-209 was also higher than the maximum concentrations of each of the other congeners.

The levels of PBDEs in the current study were lower than those reported in a pilot study in Kampala and Nakaseke districts ($\sum$PBDEs; 590–811 pg/g lw; median 1240 pg/g lw) (Matovu et al., 2019). The results of the present study were also lower than those reported in samples from other countries in Africa such as Tanzania (median; 19,800 pg/g lw) (Müller et al., 2016), South Africa (median; 1200 pg/g lw) (Darnerud et al., 2011), Tunisia (9800 pg/g lw) (Hassine et al., 2012) and Ghana (4500 pg/g lw) (Asante et al., 2011) (Table S1), and around the world. These differences can be attributed to differences in study designs and differences in possible sources of maternal exposure to PBDEs reported in the different studies. For instance, participants in the present study were those who reported no direct known occupational or non-occupational exposure to PBDEs and therefore had lower levels of PBDEs. In Tanzania, Müller et al. (2016) reported that living near industries/incinerators and mining areas, as well geophagy during pregnancy were associated with higher levels of PBDEs. Similarly, Matovu et al. (2019) reported that maternal exposure to fumes from paints was associated with higher breastmilk levels of BDE-47 while e-waste recycling was associated with higher levels of BDE-99 and -153. The results of the present study and Matovu et al. (2019) may suggest that occupational exposure contributes more to the body burdens of PBDEs amongst the

Table 2

Levels of brominated flame retardants, dioxins and PCBs (pg/g lw) in breast milk samples from Kampala, Uganda (N = 30).

Brominated flame retardants (BFRs)

Compound	DF (%)	Median	Min	Max
HBB	0			
BB-153	5(17)		<0.1	64.7
BDE-7	0			
BDE-10	0			
BDE-15	11(38)		<15	166
BDE-17				
BDE-28	6(21)		<29	280
BDE-30	0			
BDE-47	15(52)	392	<179	3661
BDE-49	17(59)	13.9	<7.6	88.5
BDE-66	16(55)	14.4	<5.6	125
BDE-71	6(21)		<0.1	11.2
BDE-77	15(52)	6.35	<0.1	21.6
BDE-85	1(3)		<4.2	14.8
BDE-99	3(10)		<76.1	257
BDE-100	7(24)		<16.8	140
BDE-119	19(66)	3.90	<0.1	25.1
BDE-126	7(24)		<2.4	26.7
BDE-138	3(10)		<0.2	27.9
BDE-139	3(10)		<0.1	15.4
BDE-140	5(17)		<0.1	13.9
BDE-153	1(3)		<40.1	299
BDE-154	0			
BDE-156	1(3)		<0.1	9.0
BDE-171	4(14)		<0.1	58.4
BDE-180	4(14)		<0.1	23.8
BDE-183	3(10)		<20.8	51.5
BDE-184	5(17)		<0.1	48.5
BDE-191	4(14)		<0.1	55.6
BDE-196	0			
BDE-197	0			
BDE-201	4(14)		<6.7	45.5
BDE-203	2(7)		<5.6	11.6
BDE-204	0			0.0
BDE-205	2(7)		<4.5	11.8
BDE-206	10(35)		<7.5	153
BDE-207	7(24)		<17.5	274
BDE-208	3(10)		<13.4	228
BDE-209	8(28)		<118	4764
$\sum$PBDEs	**28**(**97**)	**633**	**128**	**8861**

Dioxins and PCBs

Compound	DF (%)	Median	Min	Max
2,3,7,8-TeCDD	1(3)		<0.01	0.62
1,2,3,7,8-PeCDD	4(13)		<0.01	1.00
1,2,3,4,7,8-HxCDD	1(3)		<0.01	0.26
1,2,3,6,7,8-HxCDD	6(20)		<0.01	1.93
1,2,3,7,8,9-HxCDD	0			
1,2,3,4,6,7,8-HpCDD	22(73)	0.98	<0.01	5.93
1,2,3,4,6,7,8,9-OCDD	9(30)		<2.89	16.3
$\sum$PCDDs (pg/g lw)		*4.81*	*<0.01*	*22.2*
2,3,7,8-TeCDF	1(3)		<0.01	0.29
1,2,3,7,8-PeCDF	4(13)		<0.01	0.31
2,3,4,7,8-PentaCDF	25(83)	1.04	<0.01	6.47
1,2,3,4,7,8-HxCDF	19(63)	0.28	<0.01	1.96
1,2,3,6,7,8-HxCDF	20(68)	0.39	<0.01	2.18
1,2,3,7,8,9-HxCDF	0			
2,3,4,6,7,8-HxCDF	8(27)		<0.01	0.95
1,2,3,4,6,7,8-HpCDF	5(17)		<0.01	1.37
1,2,3,4,7,8,9-HpCDF	0			
1,2,3,4,6,7,8,9-OCDF	0			
$\sum$PCDFs (pg/g lw)		*1.87*	*<0.01*	*10.70*
$\sum$PCDD/Fs	**29**(**97**)	**4.45**	<**0.01**	**26.1**
WHO$_{2005}$ TEQ$_{PCDD/Fs}$		**0.40**	**0.00**	**2.59**
WHO$_{1998}$ TEQ$_{PCDD/Fs}$		**0.62**	**0.00**	**3.88**
PCB-28	5(17)		<65	282
PCB-52	0			
PCB-101	0			
PCB-138	0			
PCB-153	11(37)		<184	1719
PCB-180	13(43)		<75	704
$\sum$indicator PCBs	**18**(**60**)	**176**	<**65**	**2422**
Non-ortho PCBs				
PCB-77	10(33)		<6.7	106
PCB-81	30(100)	3.93	1.38	15.2
PCB-126	28(93)		<1.7	47.7
PCB-169	29(97)	1.6	<0.01	6.31
Mono-ortho PCBs				
PCB-105	14(47)		<55	794
PCB-114	26(87)	18.4	<0.7	157
PCB-118	3		<171	550
PCB-123	15(50)	5.29	<0.3	35.3
PCB-156	4(13)		<22.4	168
PCB-157	22(73)	11.9	<0.4	195
PCB-167	0			
PCB-189	14(47)		<0.2	144
$\sum$dl-PCBs	**30**(**100**)	**129.2**	**13.3**	**1297**
WHO$_{2005}$ TEQ$_{PCBs}$		**1.16**	**0.03**	**5.25**
WHO$_{1998}$ TEQ$_{PCBs}$		1.10	0.02	4.99
WHO$_{2005}$ TEQ$_{PCDD/Fs + PCBs}$		**1.26**	**0.07**	**7.84**
WHO$_{1998}$ TEQ$_{PCDD/Fs + PCBs}$		1.43	0.06	8.88

DF (%) = detection frequency (number of samples with concentration > LOD).

The words in bold are to emphasise the broad classes of the pollutants analysed and their total concentrations. Italics are to emphasise concentrations of sub-classes of pollutants and their total concentrations.

population in Kampala compared to dietary exposure. However, this conclusion warrants more investigation as levels of PBDEs in occupational environments in Uganda are largely understudied.

Similar to other studies (Asante et al., 2011; Müller et al., 2016), BDE-47 was the most dominant BDE congener in this study, suggesting maternal exposure to commercial penta-BDE mixture. However, the elevated levels and dominance of BDE-209 in some samples suggests exposure of mothers to deca-BDE mixture through consumer products and uncontrolled e-waste recycling activities. Since the half-life of BDE-209 (15 days) is short, this maternal exposure is recent and ongoing (Darnerud et al., 2015).

3.3. Levels of indicator PCBs, dioxin-like PCBs and PCDD/Fs

Amongst the indicator PCBs, only PCB-28, −153 and −180 were detected (Table 2). $\sum$*i*-PCBs ranged from <65–2422 pg/g lw (median; 159.5 pg/g lw). The levels of $\sum$*i*-PCBs in our study were lower than those reported in breastmilk samples in Tanzania (range; n.d-138,000 pg/g lw; median 3990 pg/g lw) (Müller et al., 2017), Tunisia (mean; 107,000–750,000 pg/g lw) (Ennaceur et al., 2008), China (3400-39,200; median 13,200 pg/g lw) (Deng et al., 2012), France (14,260–397,270 pg/g lw; median 85,190 pg/g lw), Finland (range 44,400-190,970; median 103,980 pg/g lw) and Denmark (range 57,800-967,500; median 162,800 pg/g lw) (Antignac et al., 2016). The low levels of *i*-PCBs in our samples could be attributed to the low levels of industrialization in Kampala, compared to other countries, and to the fact that participants in our study reported no occupational exposure to fumes of any kind.

PCB-153 was the major PCB congener in our study (contributed >60% to $\sum$*i*PCBs), consistent with studies on human samples in Africa (Asante et al., 2011; Ennaceur et al., 2008; Henríquez-Hernández et al., 2016), Europe (Antignac et al., 2016; Pratt et al., 2013) and Asia (Deng et al., 2012; Han et al., 2019). Higher chlorinated PCBs such as PCB-153 and PCB-180 have longer biological half-lives compared to the lower congeners (Schettgen et al., 2015). Therefore, the dominance of these congeners in human samples in Africa suggests that irregular handling of historically contaminated products and lipid-rich foods might still be responsible for environmental contamination and human exposure to PCBs in Africa.

The sum of dioxin-like PCBs ($\sum$dl-PCBs) ranged from 13.3 to 1297 pg/g lw (median; 129 pg/g lw) with a corresponding $\sum$WHO-TEQ$_{2005}$ of 0.03–5.25 pg/g lw (median; 1.16 pg TEQ/g lw). $\sum$PCDD/Fs ranged from n.d to 26.1 pg/g lw (median; 4.45 pg/g lw) with corresponding WHO$_{2005}$ TEQ values of 0.00–2.59 pg TEQ/g lw (median; 0.4 pg TEQ/g lw). The median TEQ levels of PCDD/Fs in the present study were 30.8% lower than the levels reported in the 2005–2010 WHO/UNEP breastmilk survey in Uganda (1.3 pg TEQ/g lw) (van den Berg et al., 2017), while the PCB TEQ level was 54.6% higher. The trend of PCDD/Fs is consistent with a general decrease in observed levels of dioxins worldwide following the implementation of strict regulations on dioxins (Rawn et al., 2017; van den Berg et al., 2017). $\sum$PCDD/Fs and $\sum$dl-PCBs in our study were also lower than those reported in Ghana (Bruce-Vanderpuije et al., 2020), as well as those in more industrialized areas around the world such as Canada (Rawn et al., 2017), Germany (Li et al., 2020), China (Shen et al., 2012) (Table 3). Low levels of PCDD/Fs and dl-PCBs in human milk samples can be attributed to maternal dietary habits rather than point emission sources (Schuhmacher et al., 2019). However, it should be noted that in developing countries, like Uganda, the sources of dioxin-like PCBs and PCDD/Fs are not well characterized (Ssebugere et al., 2019), which may lead to increased human exposure to the pollutants as reflected in the TEQ levels of dl-PCBs in this study. More investigations into the ambient levels of dioxins in Uganda are warranted.

The most frequently detected dl-PCB congeners were PCB-81, −169, −126, and −114 with DFs of 100%, 97.7%, 93.3%, and 86.7%, respectively. PCB-105 was detected in 46.7% of the samples, and dominated the PCB profile in these samples (contributed 52% of $\sum$dl-PCBs). For PCDDs, 1,2,3,4,7,8-HpCDD was the dominant congener, while amongst PCDFs, 2,3,4,7,8-PeCDF dominated the profile followed by 1,2,3,6,7,8-HxCDF and 1,2,3,4,7,8-HxCDF. OCDD detected in 33% of the samples and was the major PCDD/F congener in each of these samples (range; 3.0–16.3 pg/g lw). The congeners OCDD, 2,3,4,7,8-PeCDF, 1,2,3,6,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD have been reported as the dominant PCDD/Fs in breastmilk samples elsewhere, such as in Germany (Li et al., 2020).

3.4. Association of POPs with maternal age and BMI

Increase in maternal age was significantly associated with increased log-transformed levels of PCB-81 ($\rho = 0.444$; $p = 0.014$), PCB-169 ($\rho = 0.389$; $p = 0.034$), and $\sum$PCDD/Fs ($\rho = 0.424$; $p = 0.022$). No association was observed between maternal age and $\sum$PBDEs ($\rho = 0.097$, $p = 0.616$) (Table S2). Normally, body burdens of PCDD/Fs and dioxin-like compounds tend to increase with maternal age due to bioaccumulation (Antignac et al., 2016; Bruce-Vanderpuije et al., 2019; Deng et al., 2012; Giovannini et al., 2014; Lu et al., 2015). For PBDEs, the lack of such association in our study is consistent with our recent study in Uganda (Matovu et al., 2019) and can be attributed to recent, on-going exposure to the pollutants, or to differences in lifestyles in which young mothers may have higher exposure levels to the pollutants through use of computers and consumer products compared to older ones.

BMI was negatively associated with PCB-114 ($\rho = -0.376$, $p = 0.040$) but not with any other POPs. The observed lack of association for most pollutants is consistent with other studies (Matovu et al., 2019; Müller et al., 2016). Normally, a decrease in body burdens of POPs with BMI can be attributed to a dilution effect of body burdens associated with weight gain (Mannetje et al., 2013). The lack of association observed could also be due to on-going exposure of the population to POPs, or due the small sample size which lacks the statistical power to identify subtle changes in POPs levels.

3.5. Infant dietary exposure

The health risk posed to nursing infants through lactation of milk contaminated with PBDEs was previously reported in our recent study (Matovu et al., 2019). Therefore, for this study we estimated health risks posed to the nursing infants due to PCDD/Fs and dl-PCBs in breast milk. These health risks were estimated by calculation of daily dietary intake (EDI) of PCDD/Fs and dl-PCBs using Eq. (1) below, as described in Chan et al. (2007).

$$\mathrm{EDI} = \mathrm{V} \times \text{lipid content } (\%) \times \frac{\mathrm{C}}{w} \tag{1}$$

where V is the daily milk consumption (750 g), C is total WHO-TEQ concentration of the dioxins in the sample and w is the birth weight of the infant (kg). The estimated daily dietary intakes (EDIs) for PCDD/Fs and

Table 3

Comparison of levels of dl-PCBs and PCDD/Fs (pgTEQ g^{-1} lipid) reported in human breast milk samples around the world.

Area/Country	Year of sampling	N	Concentrations (pg/g lw)		WHO-TEQs$_{2005}$ (pg TEQ/g lw)		Reference
			$\sum$dl-PCBs	$\sum$PCDD/Fs	dl-PCBs	$\sum$PCDD/Fs	
Kampala, Uganda	2018	30	129 (13.3–1297)	4.45 (<0.01–26.1)	1.16 (0.03–5.25)	0.40 (0.00–2.59)	This study
Uganda	2005–2010	1 pool			0.75	1.3	van der Berg et al. (2017)
Ghana[a]	2017	21	0.15–213		1.67		Bruce-Vanderpuije et al. (2020)
Taiwan	2013–2016	25				2.7 (0.05–4.53)	Chen et al. (2018)
Guangdong province; China[a]	2017–2018	6 pools	2166 (1419-2598)	323 (167–662)	2.21	8.32	Huang et al. (2019)
China (several regions)	2011	1760	2653 (661–8450)	132 (24.8–488)	0.4–5.1[c]	2.2–8.7[c]	Zhang et al. (2016)
France	2007	44			8.31 (1.85–25.9)	9.24 (0.7–39.6)	Focant et al. (2013)
China (Zhejiang)	2008	74	1570-30,808	7.7–194	0.66–12.3	0.65–5.3	Shen et al. (2012)
Baranya, Hungary[a]	2007	22	3.93	67.8	1.04	2.13	Vigh et al. (2013)
Shanghai, China[a]	2011–2012	150	3176 (597–19,619)	78 (25–1235)	4.6 (0.75–10.2)	4.6 (0.27–16.8)	Lu et al. (2015)
Catalonia, Spain[a]	2017	20		28.8 (n.d-48.5)		2.26 (0.73–4.19)	Schuhmacher et al. (2019)
Germany	2016	99		35.7 (0.00–115)	2.43 (0.6–7.06)	2.44 (0.28–2.44)	Li et al. (2020)
Valencia, Spain	2015	75	0.40–6102	0.003–128	1.54[b]	2.58[b]	Hernández et al. (2020)
Denmark	1997–2002	438			6.55 (2.09–52.3)	13.2 (2.79–61.8)	Antignac et al. (2016)
Finland	1997–2002	22			4.63 (2.01–8.98)	9.05 (3.48–17.6)	Antignac et al. (2016)
France	2011–2014	96			4.31 (1.62–19.9)	6.07 (1.26–14.6)	Antignac et al. (2016)
Canada	2008–2011	298			1.3 (0.4–7.8)	4.9 (1.6–19)	Rawn et al. (2017)
New Zealand[a]					1.29 (0.58–3.68)	3.54 (1.39–10.8)	Mannetje et al. (2013)

Data is reported as median (range); N is number of samples analysed.

[a] Mean TEQs reported instead of median.

[b] Geom mean.

[c] TEQ$_{1998}$.

dl-PCBs and total dioxins (PCDD/Fs + dl-PCBs) were 0.06–44.5 (mean; 9.54; median 5.57) and 0.6–42.6 (mean; 16.0 and median; 13.1), and 1.24–71.1 (mean; 23.9, median; 18.3) pg TEQ/kg bw per day, respectively. The mean EDI for total dioxins (PCDD/Fs and PCBs) in the present study was lower than that reported in samples from Guangdong Province, China (47.5 pg TEQ_{2005}/kg bw per day), and in the Chinese national survey (14.2–48.6 pg TEQ_{1998}/kg bw per day) (Li et al., 2009). The EDI for dl-PCBs in the present study was higher than that reported in breastmilk samples in Ghana (mean; 4.95 pg TEQ/kg bw per day) (Bruce-Vanderpuije et al., 2020). This was due to a difference in method designs between the two studies. In the latter study, the authors assumed a constant birthweight of 7 kg and a low milk consumption rate (600 mL per day) which greatly reduced the EDIs calculated. However, the mean EDI for total dioxins (23.9 pg TEQ/kg bw per day) in the present study was still several times higher than the WHO tolerable intake (1–4 pg TEQ/kg bw per day) (van Leeuwen et al., 2000) suggesting that the breastmilk in Uganda might pose some health risks to the nursing infants with respect to PCDD/Fs and dl-PCBs. This conclusion must, however, be interpreted with caution since the WHO tolerable levels are meant for chronic exposure and not just during lactation as this covers a short period of time (van den Berg et al., 2017).

3.6. Association of breastmilk pollutant levels with TH levels

In the crude univariate models, statistically significant inverse associations were observed between T_3 and PCBs −126 and −169 ($\beta = -0.153$; 95% Confidence interval (CI): −0.291, −0.015 and β −0.143; CI: −0.260, −0.026, respectively), and with $\sum TEQ_{PCB}$ ($\beta = -0.164$; CI: −0.315, −0.012). rT_3 was significantly positively associated with 1,2,3,4,6,7,8-HpCDF, $\sum$dl-PCBs and $\sum TEQ_{PCDD/Fs}$ ($\beta = 0.105$–0.127; $p = 0.004$–0.05), while no significant associations were observed between T_4 and the maternal burdens of organohalogen pollutants (Table 4). After adjustment for maternal age, only inverse associations between T_3 and the levels of PCB-126, PCB-169, and $\sum TEQ_{PCBs}$ persisted. For rT_3, positive association with 1,2,3,4,7,8-HpCDF persisted. Hierarchical cluster analysis generated three groups of POPs (Fig. 1) which were then represented by PCB-126, $\sum TEQ_{PCDD/Fs}$, and $\sum$dl-PCBs in the multivariate model. None of the clusters of POPs showed any significant associations with THs (Table S4).

Breastmilk is the main nutritional source of THs to the nursing infants in the first few months of postpartum (Ilcol et al., 2006). However, our study supported the idea that PCDD/Fs and dl-PCBs may alter breastmilk levels of circulating THs. Hence, maternal exposure to PCDD/Fs and dl-PCBs is likely lower than the levels of THs transferred from the mother to the neonates during lactation, which may lead to adverse effects in the nursing infants. It should be noted that TH levels influence energy homeostasis, as well as metabolic and organ development processes in infants (Berg et al., 2017; Lignell et al., 2013).

Our findings were consistent with studies elsewhere. For instance, Sweden, Koopman-Esseboom et al. (1994) reported negative associations between PCDD/Fs and dl-PCB levels in breastmilk and maternal total T_3 and T_4 levels in late pregnancy. In Korea, Kim et al. (2013) showed that PCB-118 was associated with increased odds of lower levels of (free and total) T_3, $\sum$PCB with total T_3 and total T_4, while PCB-28 was associated with higher odds of lower total T_4 in blood serum of pregnant mothers. Positive association between rT_3 (and T_4), with PCBs and PCDD/Fs was also reported in German breastmilk samples (Li et al., 2020). PCBs and their metabolites (such as hydroxylated PCBs) alter thyroid hormone homeostasis through competitive binding onto common thyroid hormone receptors as a result of their structural similarity to THs (Boas et al., 2012; Ghassabian and Trasande, 2018). However, the associations should be interpreted with care since similar studies have suggested that the relationship between PCBs and THs may be influenced by the presence of other POPs such as PCDD/Fs (Jacobson et al., 2017; Li et al., 2020).

We could not establish any significant associations between breastmilk $\sum$PBDE levels and THs (Table S2). Our findings were consistent with a recent study (Han et al., 2019) in which no associations were observed between serum levels of $\sum$PBDEs and THs in a Chinese population. However, our results were inconsistent with a recent study in Germany (Li et al., 2020). The authors found that breastmilk levels of PBDEs (BDE-28, −47, −99, −100, −154, −183, and −197) were inversely associated with T_4 and rT_3, while in adjusted single-pollutant models, T_4 was inversely associated with BDE-99, −154, and −196; T_3 was inversely associated with levels of BDE-47, −99, −100, −197, −203, −207; and rT_3 was inversely associated with levels of BDE-47, −99, −183, and −203. The study suggested that low level exposure to PBDEs may lead to disruption of thyroid hormone homeostasis.

Generally, PBDEs influence maternal thyroid hormone levels by interfering with TH transport and metabolism (Li et al., 2020). For example, PBDEs induce hepatic enzymes responsible for glucuronidation, or down-regulate transmembral TH transport (Boas et al., 2012; Ghassabian and Trasande, 2018). Moreover, their hydroxylated metabolites may competitively bind as agonists or antagonists to TH receptors (Ren et al., 2013). It should be noted that associations between levels of PBDEs and THs may be dependent on exposure levels and may approximate a U-shaped curve (Zhao et al., 2015). It is not clear why no significant associations could be established between PBDE levels and THs in the present study, yet our levels were even lower than those reported by Li et al. (2020). However, Lignell et al. (2016) reported that in a low-exposure population, PBDEs may influence thyroid hormone levels only in the early stages (first trimester) of pregnancy but not in the later stages. Since our milk concentrations of THs and PBDEs have been determined in the first few days postpartum, the levels may be used a measure of circulating levels in

Table 4
Associations of breastmilk levels of POPs with THs.

	Regression coefficient (β)	*p*-value	95% CI for β	Regression coefficients (β)	*p*-value	95% CI for β
	Crude model			Adjusted for maternal age		
	T3			**T3**		
PCB-126	-0.153^{**}	0.031	−0.291, −0.015	-0.153^{**}	0.034	−0.293, −0.013
PCB-169	-0.143^{**}	0.018	−0.260, −0.026	-0.170^{*}	0.009	−0.294, −0.046
$\sum PCB_{TEQ}$	-0.164^{**}	0.035	−0.315, −0.012	-0.170^{**}	0.033	−0.325, −0.015
$\sum PCDD/F_{TEQ}$	−0.098	0.059	−0.201, 0.004	-0.107^{**}	0.049	−0.213, 0.000
2,3,4,7,8-PeCDD	−0.071	0.104	−0.157, 0.016	−0.076	0.092	−0.166,0.013
	T4			**T4**		
PCB-157	0.065	0.09	−0.011, 0.141	0.063	0.115	−0.017, 0.143
	rT3			**rT3**		
1,2,3,4,6,7,8-HpCDF	0.105	0.004^{*}	0.036, 0.173	0.101	0.007^{**}	0.030, 0.171
$\sum$dl-PCBs	0.127	0.05	0.000, 0.253	0.121	0.062	−0.007, 0.249
$\sum PCDD/F_{TEQ}$	0.114	0.034^{**}	0.009, 0.219	0.107	0.055	−0.003, 0.216

CI = confidence interval.

* Associations are significant at $p < 0.01$.

** Associations are significant at $p < 0.05$.

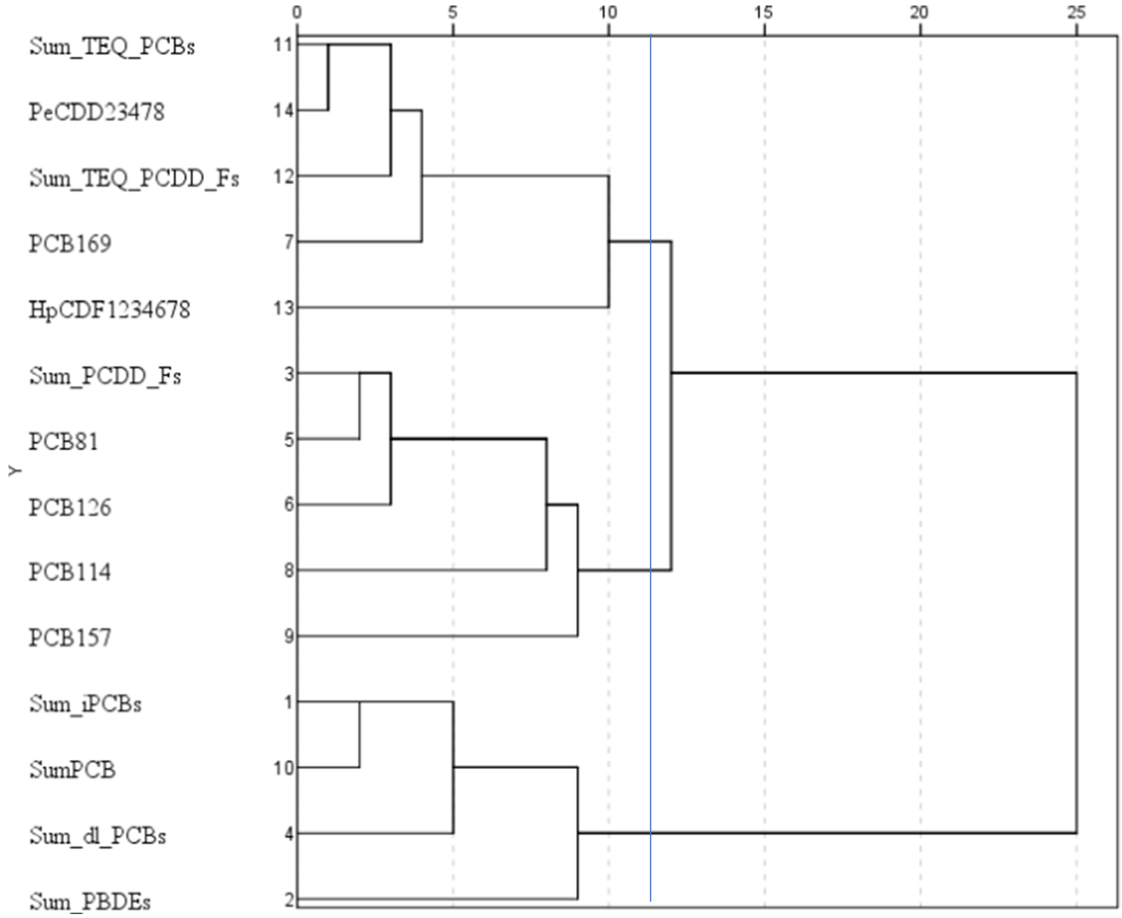

Fig. 1. Hierarchical clustering of POPs based on correlations between the compounds (the blue line represents the manually selected cut-off for the number of clusters).

late pregnancy to corroborate the findings by Lignell et al. (2016). More studies to investigate the influence of maternal burdens of POPs and THs in late pregnancy and during the first few days of postpartum are needed.

Differences in study designs might also be responsible for the observed lack of association between POPs and THs in the multivariate models. For instance, our samples size was small, and the time at which we carried out the sampling (2–9 days postpartum) was significantly different from Li et al. (2020). In addition, the observed associations might have been influenced by maternal thyroid status due to reverse causality. It has been suggested that maternal T_3 status in late pregnancy may influence distribution, metabolism and excretion of the contaminants by affecting mammary gland transfer of the POPs from maternal blood into breastmilk (Lignell et al., 2016), which consequently affects the lipid levels detected in maternal milk and the observed associations with THs.

4. Conclusions

This is the first study to report levels of PCBs, PCDD/Fs, HBB and BB-153 in individual breastmilk samples from Uganda. The median concentration of $\sum i$PCBs was 176 pg/g lw, HBB was not detected in any of the samples while the maximum level of BB-153 was 64.7 pg/g lw. Similarly, the levels of $\sum$PBDEs, PCDD/Fs and dl-PCBs in this study (median; 392 pg/g lw, 0.4 pg TEQ/g lw and 1.16 pg TEQ/g lw) were lower than those reported in other developing and developed countries elsewhere. However, based on WHO tolerable limits, calculations of EDIs showed potential health risks to nursing infants associated with consumption of breastmilk in Uganda with respect to PCDD/Fs and dl-PCBs. Our findings also suggested that background levels of POPs could influence maternal thyroid hormone levels. However, our study has several limitations: First, the sampling was done manually, hence, it is possible that the samples were contaminated with dust from the hospital equipment which might have affected the results. The use of field blanks is recommended in future studies. Secondly, the present study is limited by the small sample size compared to other studies (Kim et al., 2013; Li et al., 2020). In a small population such as ours, subtle changes in THs may be undetectable since intra-individual variations may be negligible compared to inter-individual variations or wide reference ranges (Boas et al., 2012). In addition, we did not evaluate the participants' iodine status which might influence the circulatory levels of THs (Kim et al., 2013). We recommend a study with a bigger sample size to assess the temporal influence of maternal levels of POPs on THs during lactation.

CRediT authorship contribution statement

Henry Matovu: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Zhong-Min Li:** Methodology, Formal analysis, Investigation, Writing – review & editing. **Bernhard Henkelmann:** Formal analysis, Investigation, Writing – review & editing. **Silke Bernhöft:** Formal analysis, Investigation, Writing – review & editing. **Meri De Angelis:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Karl-Werner Schramm:** Supervision, Funding acquisition, Writing – review & editing. **Mika Sillanpää:** Supervision, Funding acquisition, Writing – review & editing. **Charles Drago Kato:** Conceptualization, Writing – review & editing. **Patrick Ssebugere:** Conceptualization, Formal analysis, Investigation,

Methodology, Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the mothers who participated in the study, and physicians (Harriet Solomy Nababiito, Hadijah Nakyobe, Brendah Luzze, Margret Akello, Jacinta Nalule) at St Francis Hospital Nsambya for their assistance during sample collection. We also acknowledge the financial support from the Swedish International Development Agency (grant number 51180060), the Presidential Scientific Initiative on Epidemics (PRESIDE), Carnegie Corporation of New York (grant number G-16-54068), and Third World Academy of Sciences (20-267 RG/CHE/AF/AC_G). Patrick Ssebugere is thankful to the TWAS-DFG fellowship programme for funding his 3 months (Jan-April 2019) stay at Helmholtz Zentrum Muenchen. Zhong-Min Li was supported by the China Scholarship Council (No. 201604910584). The authors would like to thank Agilent Technologies for supporting this research project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.145262.

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