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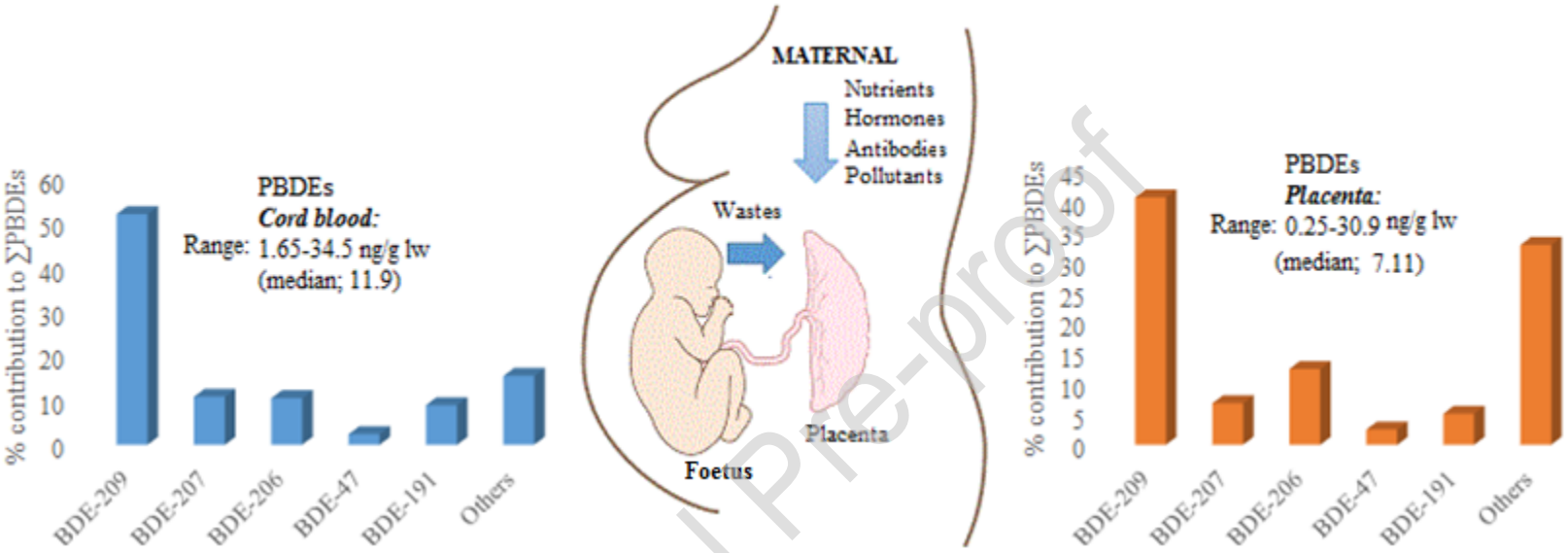
GRAPHICAL ABSTRACT



Prenatal exposure levels of polybrominated diphenyl ethers in mother-infant pairs and their transplacental transfer characteristics in Uganda (East Africa)

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Abstract

Polybrominated diphenyl ethers (PBDEs) are ubiquitous environmental pollutants with adverse effects on the foetus and infants. This study aimed at assessing *in utero* exposure levels and transplacental transfer (TPT) characteristics of BDE congeners in primiparous mothers from Kampala, the capital city of Uganda. Paired human samples (30 placenta and 30 cord blood samples) were collected between April and June, 2018; and analysed for a suite of 24 tri- to deca-BDE congeners. Extraction was carried out using liquid-liquid extraction and sonication for cord blood and placenta samples, respectively. Clean-up was done on a solid phase (SPE) column and analysis was performed using gas chromatography/mass spectrometry (GC/MS). Total (∑) PBDEs were 0.25-30.9 ng/g lipid weight (lw) (median; 7.11 ng/g lw) in placental tissues and 1.65-34.5 ng/g lw (median; 11.9 ng/g lw) in cord blood serum, with a mean difference of 1.26 ng/g lw between the compartments. Statistical analysis showed no significant difference between the levels of PBDEs in cord blood and placenta samples (Wilcoxon signed

rank test, p = 0.665), possibly because foetus and neonates have poorly developed systems to metabolise the pollutants from the mothers. BDE-209 was the dominant congener in both matrices (contributed 40.5% and 51.2% to ∑PBDEs in placenta and cord blood, respectively), suggesting recent and on-going maternal exposure to deca-BDE formulation. Non-significant associations were observed between ∑PBDEs in maternal placenta and maternal age, household income, pre-pregnancy body mass index (BMI), and beef/fish consumption. This suggested on-going exposure to PBDEs through multiple sources such as dust from indoor/outdoor environments and, ingestion of other foods. Based on absolute concentrations, the extent of transplacental transport was greater for higher congeners (BDE-209, -206 and -207) than for lower ones (such as BDE-47), suggesting alternative TPT mechanisms besides passive diffusion. More studies with bigger sample sizes are required to confirm these findings.

Capsule: Transplacental transport is higher for highly brominated diphenyl ether congeners (BDE-209, 206 and 207) than for lower ones (such as BDE-47) in Uganda.

Keywords

Prenatal exposure; PBDEs; Transplacental transfer; Cord blood; Uganda

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of brominated compounds used as flame retardants in many household and commercial products such as electronic products, furniture, plastics and textiles (Frederiksen et al., 2009; Lopez-Espinosa et al., 2015; Lyche et al., 2015). Commercially, PBDEs are produced as deca-, octa- and penta-BDE formulations. The penta-BDE formulation primarily consists of BDE-47 and -99; the octa-BDE formulation consists of a mixture of hexa- to nona-BDEs, while the deca-formulation comprises 98% BDE-209 and

various nona-BDEs (Miller et al., 2012). PBDEs are persistent, lipophilic, bio-accumulative and toxic to living organisms (Abballe et al., 2008; Arinaitwe et al., 2014; Fromme et al., 2016; Ni et al., 2013). As a result, the compounds have been listed for elimination by the Stockholm Convention on persistent organic pollutants (POPs) (Stockholm Convention, 2019). Uganda ratified the convention on 20th July 2004, thereby pledging its commitment to protect the environment and humans from toxic chemicals of global concern.

Usage of the penta-BDE formulation has been banned in many countries worldwide since 2004 but the deca-formulation continued to be used until 2013 (Darnerud et al., 2015; Guo et al., 2016). The continued use and/or recycling of consumer products containing PBDEs may be exposing mothers to the chemicals (Vuong et al., 2018). Exposure to PBDEs mainly occurs through ingestion of PBDE contaminated food and inhalation of dust particles (Fraser et al., 2009; Jones-Otazo et al., 2005; Matovu et al., 2019). Epidemiological studies have reported that maternal exposure to PBDEs can result in foetal exposure through transplacental transport (TPT) by measurement of the pollutants in cord blood (Antignac et al., 2009; Chen et al., 2014; Lin et al., 2011), amniotic fluid (Miller et al., 2012), meconium (Jeong et al., 2016; Woźniak et al., 2018), neonatal urine (Chen et al., 2014) and paediatric hair (Aleksa et al., 2012).

The human placenta is an organ responsible for the circulation of nutrients, gases and waste products between the mother and foetus. Mother-to-foetus transplacental exchange occurs through diffusion, active transport, osmosis and vesicular transport (Kim et al., 2015; Zhao et al., 2018). Maternal exposure to the chemicals during pregnancy can enhance the production of pro-inflamatory cytokines by the placenta, thereby increasing the risk of infection-mediated preterm birth (Peltier et al., 2012). In addition, *in utero* exposure to PBDEs has been linked to a broad range of adverse effects on the foetus such as neurodevelopmental toxicity (Costa and Giordano,

2007; Cowell et al., 2018) and may result in lower birth outcomes such as birth weight, birth length and chest circumference (Chao et al., 2007; Lignell et al., 2013; Lopez-Espinosa et al., 2015). Mechanisms explaining the adverse effects of prenatal PBDE exposure on foetal growth remain unclear but may involve alteration in levels of thyroid hormones by disrupting thyroid hormone homeostasis (Lignell et al., 2013), as well as alterations in placental DNA methylation (Zhao et al., 2016).

In developing countries, increased industrial activities and poor electronic-waste management practices could be directly or indirectly exposing the population to POPs such as PBDEs (Ssebugere et al., 2019). A recent study in Tanzania reported that organohalogen pollutants were ubiquitous in maternal and foetal samples from Arusha (Müller et al., 2019). However, *in utero* exposure levels and profiles of POPs in Kampala, the most urbanised and industrialised city in Uganda, remain unknown. This study aimed at assessing the levels and TPT characteristics of PBDEs in paired maternal placenta and cord blood samples from Kampala. The data is important in evaluating the effectiveness of the implementation of the Stockholm Convention in Uganda since its adoption in 2004.

2. Materials and methods

2.1. Ethical considerations and study population

The study was approved by the Research and Ethics Committee of the Uganda National Council of Science and Technology (approval number HS 2263), and St. Francis Hospital Nsambya, Uganda. The goals and requirements of the study were clearly explained to all participants and they were requested to sign a consent form. All information collected from the mothers was kept confidential.

The participants were identified during their prenatal visits to St. Francis Hospital Nsambya, Uganda (Fig. 1). A total of 30 mothers were recruited to the study. All were healthy, primiparous, non-smokers and older than 16 years. Pregnancies were full-term, and no medical problems had been detected during pregnancy. In addition, participants were those who had lived in Kampala for the last five years.

2.2. Sample collection

Data about the maternal and neonatal characteristics was collected using a questionnaire at the time of sampling. Placentas and cord blood samples were collected immediately after delivery. Maternal sera could not be collected due to inconsistencies in the mothers' visits to the hospital. Besides, placental concentrations of environmental pollutants reflect accumulation at the barrier, while those in cord blood reflect the extent of transplacental transfer (Needham et al., 2011). A total of 30 placenta and 30 cord blood matched samples were collected by physicians. At least 20 mL of cord blood from each donor mother was collected in EDTA vacutainer. The blood was centrifuged and the plasma was transferred into labelled cryo vials. Placenta tissues were cleaned free of cord blood using distilled water and then transferred into labelled sterile polypropylene tubes. The vials and tubes containing the samples were transferred into zip-lock bags and shipped in a UN box packed with dry ice to the Eurofins environmental laboratory (Finland), where they were stored at -20^{o}C to avoid microbial degradation before extraction.

2.3. Chemicals and standards

Target analytes were 24 PBDE congeners (IUPAC numbers 15, 17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 138, 153, 154, 156, 183, 184, 191, 197, 206, 207 and 209). Chemical standards were purchased from Cambridge Isotope Laboratories (Andover, MA, USA), Accustandard

(New Haven, CT, USA) and Wellington Laboratories (Guelph, ON, Canada). *n*-hexane, dichloromethane (DCM), hydrochloric acid (35-37%), methyl tert-butyl ether, 2-propanol, sulfuric acid (98%), aluminium oxide and silica gel were supplied by Merck (Darmstadt, Germany), and anhydrous sodium sulfate by J.T. Baker (Deventer, the Netherlands). All solvents used were of trace analysis grade.

2.4. Analytical procedure

2.4.1. Extraction of cord blood samples

Extraction of cord blood was done as reported by Chen et al. (2014). Briefly, cord blood plasma was allowed to thaw and 3 g was transferred into a clean centrifuge tube. The sample was then spiked with known amounts of surrogates (1 ng each of 4-fluoro-2,3,4,5-tetrabromodiphenyl ether (F-BDE-69) and ^{13}C-BDE-209) and equilibrated overnight. 1 ml of hydrochloric acid (6M) was then added to the mixture followed by 5 ml of 2-propanol. The sample was subsequently extracted three times with 5 ml of a mixture of *n*-hexane/methyl tert-butyl ether (1:1 v/v). The organic extracts were combined and concentrated to 5 ml using a rotary evaporator. The solvent was further evaporated off using a gentle stream of nitrogen, and whole extracts were used to determine the lipid content gravimetrically. The lipid in the flask was then reconstituted into 1 ml with *n*-hexane and kept for clean-up.

2.4.2 Extraction of placental tissues

Extraction of placenta samples followed a method reported by Leonetti et al. (2016) with minor modifications. Briefly, the placenta samples were defrosted, freeze-dried and homogenised into a fine powder using a mortar and pestle. A mixture of *n*-hexane/dichloromethane (1:1 v/v, 15 ml) was added and the samples left overnight. The samples were then spiked with 1 ng each of F-BDE-69 and ^{13}C-BDE-209 as internal standards, ultra-sonicated for 10 min and centrifuged. The

127 solvent was decanted off into a separate tube. The extraction step was then repeated twice, and
128 the extracts were combined in a clean 50-ml glass centrifuge tube. After extraction, the extracts
129 were concentrated to 1 ml using a gentle stream of nitrogen gas and the lipid content determined
130 by the gravimetric method. After lipid determination the contents in the flask were reconstituted
131 into 1 ml of *n*-hexane and kept for clean-up.

132 *2.4.3. Clean-up of sample extracts*

133 The clean-up of extracts was performed according to Frederiksen et al. (2009). The extracts were
134 loaded onto a multi-layer glass column packed from bottom to top with 5 g of deactivated
135 aluminium oxide with 10% water, 1 g activated silica (activated at 160 ^{o}C for 24 h), 5 g of silica
136 impregnated with 40% concentrated sulfuric acid, and 1 g of anhydrous Na_2SO_4. The columns
137 were conditioned with 15 mL of a mixture of *n*-hexane/dichloromethane (4:1 v/v) and eluted
138 with 30 mL of the solvent system. The resulting eluate was concentrated to a final volume of 100
139 µl using a gentle stream of nitrogen, transferred to 200 µl glass vials and spiked with 1 ng each
140 of isotope-labelled internal standards (^{13}C-labelled BDE-15, ^{13}C-labelled BDE-28, ^{13}C-labelled
141 BDE-153, and ^{13}C-labelled BDE-197) prior to analysis.

142 *2.4.4. Instrumental analysis*

143 The analytes were quantified using the isotope-dilution method, and an Agilent 7890 gas
144 chromatograph coupled with an Agilent 7010 triple quadruple mass spectrometer (MS). The MS
145 was operated in electron capture negative ionisation (ECNI) and selected ion monitoring (SIM)
146 modes. 1 µl of sample was automatically injected in each run. Chromatographic separation was
147 achieved on a DB-5 HT column (15 m × 0.25 mm internal diameter × 0.25 µm film thickness).
148 Helium gas (99.99%) was used as the carrier gas at a flow rate of 1 ml/min and methane as a
149 buffer gas. The temperature programme was set as follows: initial oven temperature was 80 ^{0}C

for 1 min; this was increased to 110 ^{0}C at 10 ^{0}C/min and further to 310 ^{0}C at 20 ^{0}C/min. This was maintained for 10 min with a post-run for 1.99 min.

2.5. Quality assurance/Quality control

A laboratory blank was run for every batch of 5 samples. All sample concentrations were blank-corrected. To assess the recovery efficiency of the extraction methods, percentage recoveries of the internal standards were calculated for all samples and blanks. The mean percentage recoveries for F-BDE-69 and ^{13}C-BDE-209 were 81±13% and 91± 8%, respectively. Since appreciable recoveries were obtained, the sample levels were not corrected for recoveries. Limits of detection (LODs) were estimated for each analyte as three times the standard deviation of the laboratory blank values. LODs ranged from 0.04 to 0.3 ng/g lw in cord blood plasma and 0.01 to 0.2 ng/g lw in placenta samples, respectively.

2.6. Data treatment and statistical analysis

The concentrations of the congeners in the maternal/foetal compartments were lipid-based. Congener levels <LOD were taken as ½ LOD during statistical analysis. The normality of data was assessed using the Kolmogorov-Smirnov test. Since the lipid-adjusted levels were not normally distributed, potential differences in PBDE levels between maternal placentas and cord blood were analysed using the Wilcoxon matched-pairs signed-rank test, while cord serum levels of PBDEs in male and female infants were compared using the non-parametric Mann-Whitney U test. In addition, Spearman rank correlation was used to determine associations between the PBDE levels and maternal/infant demographic characteristics. Observational comparison of lipid-based concentrations of the BDE congeners in cord blood and maternal placenta (Müller et al., 2019) was done to evaluate the extent of transplacental transport of the chemicals. For this purpose, only congeners detectable above LOD in at least five paired samples were considered.

In all cases, a p value <0.05 was considered statistically significant. All statistical analyses were carried out using SPSS 21.0 software for Windows (Chicago, IL, USA).

3. Results and discussion

3.1. Maternal/infant characteristics

The demographic characteristics of the donor mothers and their infants are summarised in **Table 1**. Maternal age was in the range of 17-38 years. Pre-pregnancy body mass index (BMI) varied from 22.4 to 41.8 kg/m^2. There was no significant association between maternal age and BMI (Spearman's rho, $\rho = 0.163$, $p = 0.390$). The average infant birth weight was 3.39 kg (median; 3.45 kg) and this was strongly positively associated with maternal weight ($\rho = 0.416$, $p = 0.022$). 25 mothers (83.3%) reported a monthly household income of at least 136 USD. The mothers also reported mixed diets during pregnancy. Weekly beef and fish consumption of at least three times a week was reported in 73.4% and 46.6% of the mothers, respectively.

3.2. PBDEs in maternal placenta and cord blood serum

Lipid-adjusted levels of PBDEs in placenta and cord blood are shown in **Table 2**. Total ($\sum$) PBDEs for 24 congeners ranged from 0.25 to 30.9 ng/g lipid weight (lw) (median; 7.11 ng/g lw), and 1.65 to 34.5 ng/g lw (11.9 ng/g lw) in placenta and cord blood serum, respectively. Although the levels in cord blood appeared to be higher (mean difference; 1.26 ng/g lw), statistical analysis showed no significant difference between the levels of total PBDEs in the cord blood and placental samples (Wilcoxon signed rank test: $Z = -0.433$, $p = 0.665$). In addition, no significant difference was observed between the major congeners BDEs 183, 184, 191, 207, 209 and total PBDEs in cord serum of female and male infants (Mann-Whitney U test, p = 0.185-0.467).

The differences in the detected BDE congeners made it difficult to compare our results with those from other countries, but comparisons of the levels of the most commonly detected congeners around the world are shown in Tables **3** and **4** for placenta and cord blood samples, respectively. For placenta, the ∑PBDEs in this report were in the same range of data as that reported in Tanzania (median of $\sum_{11}$PBDEs; 11.7 ng/g lw) (Müller et al, 2019), South Korea ($\sum_{24}$; 11.7 ng/g lw) (Jeong et al., 2018) and China ($\sum_{9}$; 7.0 ng/g lw) (Zhao et al., 2013). The levels in the present study were, however, higher than those reported in Finland ($\sum_{16}$; 1.04 ng/g lw) (Leino et al., 2013) and Spain ($\sum_{14}$; 2.3 ng/g lw) (Vizcaino et al., 2014) (**Table 3**).

For cord blood sera, the ∑PBDEs in this study were higher than those reported in Tanzania (Müller et al., 2019). The authors reported non-detectable median levels for $\sum_{11}$PBDEs. In addition, the median ∑PBDEs in Sweden, Denmark and Taiwan were 0.88, 0.9 and 4.63 ng/g lw, respectively, which were lower than the levels in the present study. Our results were in the same range of data as that reported in Spain and South Korea, but were lower than those reported in China (**Table 4**). The differences in levels of PBDEs within countries can be attributed to differences in exposure sources.

In the present study, the major congeners in placenta tissues were BDE-209, -206 and -196 (contributed 40.5%, 12.4% and 9.5% to $\sum_{24}$PBDEs, respectively) (**Fig. 2**). Previously published data reported BDE-209 as the most abundant congener in human placenta in Europe, Japan, China and Korea (Frederiksen et al., 2009; Gómara et al., 2007; Jeong et al., 2018; Takasuga et al., 2006; Zhao et al.,2013), while BDE-47 was the major congener in USA samples (Nanes et al., 2014; Zota et al., 2018). In a recent study in neighbouring Tanzania, BDE-99 and -47 were reported to be the dominant congeners in maternal placenta tissues (Müller et al., 2019). High proportions of BDE-209 in our placental samples could be associated with the ingestion of

contaminated food and house dust inhalation. Elsewhere, earlier studies have reported that house dust is an important exposure route to BDEs, particularly BDE-209 (Coakley et al., 2013; Schecter et al., 2005). Further studies in Uganda are warranted.

For cord blood sera, BDE-209 was the most abundant congener (contributing 51.9% to $\sum_{24}$PBDEs). This was followed by nona-BDE-207 (10.8%) and -206 (10.5%) and, octa-BDE-191 (8.93%) (**Fig. 2**). This congener profile was inconsistent with a number of studies in which BDE-47 was a major congener in cord blood samples (Foster et al., 2011; Kim et al., 2009; Kim et al., 2012; Vizcaino et al., 2011). However, a study by Zhao et al. (2016) reported that BDE-209, 207 and 206 dominated the profile of PBDEs in cord blood from China, contributing >50%, 8% and 7% to the ∑PBDEs, respectively. Another study by Antignac et al. (2009) found that the median levels of highly brominated (nona- and deca-) BDEs in cord blood samples from France were higher than those of the tri- to hepta-BDEs (0.69 ng/g lw for the latter and 12.34 ng/g lw for the former). Although BDE-209 dominated our cord blood samples, the median level of BDE-209 in the present study (7.95 ng/g lw) was less than the median levels of the congener in France (27.1 ng/g lw) and China (71.9 ng/g lw), but higher than those reported in Danish and Spanish samples (**Table 4**).

The difference in usage patterns of PBDE-containing commercial products in the different areas around the world could be responsible for the observed difference in congener patterns. Due to the importation of large volumes of products such as e-waste from Asia, mothers in Uganda are likely to be recently and continuously exposed to products containing deca-BDE formulation, either through direct usage or the recycling of used products. Furthermore, the large variation in the PBDE levels across countries may be due to interpersonal differences in exposure levels, as well as variations in placental sizes. Recently, Zhao et al. (2018) determined levels of PBDEs in

placenta samples in China and correlated them with placenta size. Their results showed that PBDE concentrations were significantly associated with lower placental length, breadth and surface area. The relationship between placental levels of PBDEs and placental dimensions in Ugandan mothers needs further investigation.

The lack of statistical difference in levels between maternal and neonatal compartments could be attributable to the low metabolic capacity of the foetus (Foster et al., 2011), since their systems are not fully developed to breakdown pollutants from the mother. In addition, a lack of statistical difference in cord blood levels of congeners between male and female neonates was observed in this study. In a related study, Choi et al. (2014) reported higher PBDE levels in cord blood for male infants (n = 54) than for female infants (n = 55). The lack of association between PBDE levels and infant sex in our study could be a result of the small sample size. However, Zhang et al. (2017) did not find any significant differences in cord blood levels of PAHs for the different infant sexes. Therefore, it is not clear whether metabolism of organic pollutants such as PBDEs and PAHs is sex specific, so more studies are needed to investigate these relationships.

Overall, metabolic capacity is of utmost importance in metabolising pollutants such as PBDEs. Previously published literature showed that, in the human placenta and foetus, PBDE exposures are associated with the expression of mRNA coding for specific CYPs such as CYP2E1, which is a xenophobic metabolising enzyme actively involved in diverse endogenous roles in fatty acid and steroid metabolic pathways (Zota et al., 2018). Further to this, CYP mRNAs are associated with enzyme activity and their expression is highly correlated with the expression of thyroid hormone-regulated genes in human tissues such as the placenta (Giera et al., 2011; Wadzinski et al., 2014). This suggests that inducible metabolic enzymes in the placenta may bioactivate

PBDEs, which can interact with TH receptor, as is the case with other organic pollutants (Giera et al., 2011).

3.3. Effect of diet and other maternal characteristics on placental PBDEs levels

In this study, ∑PBDEs in maternal placenta samples were poorly associated with maternal age (ρ = -0.291, p = 0.118), household income (ρ = -0.257 p =0.170) and maternal BMI (ρ = -0.099, p = 0.601). The poor association between PBDE levels in human samples and maternal age has been reported elsewhere (Dimitriadou et al., 2016; Herbstman et al., 2007; Matovu et al., 2019; Müller et al., 2016) and can be attributed to recent and on-going exposure to PBDEs in the general population through consumer products. Similarly, poor association between levels of POPs and BMI such as those observed in this study can be attributed to the dilution effect of body burdens of POPs during weight gain (Mannetje et al., 2013).

Previous studies have also shown that the ingestion of contaminated food, especially that of animal origin, is a major human exposure route to PBDEs (Babalola and Adeyi, 2018; Domingo et al., 2008; Pietron et al., 2019; Thomsen et al., 2008). The present study observed non-significant correlations between fish consumption and ∑PBDE levels in maternal placenta samples (ρ = 0.112, p = 0.554). Similarly, associations between placental ∑PBDEs and beef consumption were weak and non-significant (ρ = 0.214, p = 0.257). These poor associations may be ascribed to inter-individual variability in the absorption and metabolism of the pollutants. Furthermore, contributions from multiple sources of PBDEs such as other food stuffs and indoor and outdoor exposure may also be responsible for the lack of correlation. For instance, in our recent study (Matovu et al., 2019), higher rates of egg consumption were associated with higher breast milk levels of BDE-153. Hence, further investigation of the levels of pollutants in other

foods, as well as indoor and outdoor dust samples in Uganda is warranted, as these multiple sources of pollutants could be affecting their variability in human samples.

3.4. Transplacental transport of PBDEs

The low detection levels of POPs in cord blood samples previously reported in many studies suggest that the placenta membrane may act as a barrier to the transfer of POPs from the mother to the foetus, especially for the highly brominated congeners (Müller et al., 2019; Vizcaino et al., 2014). However, the placenta may not be an effective barrier and the extent of transplacental transport (TPT) of PBDEs is usually higher than that for placental retention (Foster et al., 2011; Li et al., 2013; Zhao et al., 2013; Zheng et al., 2017).

Normally, the transplacental transfer characteristics of organohalogen pollutants are evaluated using their concentration ratios between compartments such as; cord blood and the placenta and; cord blood and maternal blood, with ratios >1 indicating a higher extent of transplacental transfer (Müller et al., 2019; Needham et al., 2011; Vizcaino et al., 2014). However, the ratios are calculated for congeners with a correlation coefficient of 0.7 or higher in the matched samples (Müller et al., 2019; Vizcaino et al., 2014). In our study, because of the small number of pairs, none of the congeners met this criterion. Hence, only observational comparisons of the levels were done. Higher levels of BDEs 209, 206, 191 and 184 were observed in cord blood than in the maternal placentas. This result agreed with earlier studies (Antignac et al., 2007; Gomara et al., 2007; Li et al., 2013; Vizcaino et al., 2014). BDEs 17, 47, 138 and 153 occurred at higher levels in the placenta than in cord blood. The dominance of highly brominated congeners in cord blood in the present study suggested that transplacental transfer was higher for the higher congeners than for the lower ones.

Generally, mechanisms explaining the TPT of organic pollutants remain unclear but may include passive diffusion along with maternal lipids and the catabolic redistribution of maternal lipid stores during the final trimester of gestation (Balakrishnan et al., 2010; Foster et al., 2011; Kim et al., 2015; Mazdai et al, 2003). Based on the assumption of passive diffusion, previous studies have reported that the TPT of PBDEs decreases with an increase in the degree of bromination of the congeners (Frederiksen et al., 2010; Kim et al., 2012; Needham et al., 2011; Zheng et al., 2017). The poor membrane permeability of the highly brominated congeners can be attributed to the increasing affinity for the placenta tissue with increasing $\log K_{ow,}$ making these congeners less bioavailable. Therefore, the placental membrane should restrict the TPT of higher congeners, but this generalisation might need further investigation as several authors (Kim et al., 2012; Needham et al., 2011; Zheng et al., 2017) did not analyse for the highly brominated nona- and deca-BDEs. Moreover, Chen et al. (2014) reported that the extent of the TPT of BDE-196 and -197 was higher than that of lower brominated congeners such as BDE-47. In China, Li et al. (2013) and Zhao et al. (2018) reported that levels of BDE-209, -206 and -207 in cord blood were several magnitudes higher than those of BDE-47; suggesting a contradicting increase in TPT with a degree of bromination. It becomes apparent that, in addition to passive diffusion, active mechanisms such as the transport of enzymes through membranes may also be responsible for the TPT of PBDEs which could lead to their accumulation in cord blood, as is the case with thyroid hormone (Chen et al., 2014; Kim et al., 2015; Vizcaino et al., 2014).

Thyroid hormone (TH) can be transferred into foetal circulation by membrane transporters such as MCT8, MCT10, OATP1A2, OATP4A1, LAT1 and LAT2. In addition, TH can bind with proteins such as transthyretin and albumin produced in placental tissues (Patel et al., 2011). Since PBDEs have structural similarities with TH and a strong affinity for TH receptors, it is

possible that they have similar TPT mechanisms (Chen et al., 2014; Kim et al., 2015; Zota et al., 2011). Furthermore, negative associations of TH and PBDE levels in cord blood have been clearly documented (Abdelouahab et al., 2013; Lin et al., 2011). These associations can be explained by the competitive binding of PBDEs to thyroid binding proteins (Jeong et al., 2016), and can lead to insufficient thyroid hormones in the foetal compartment (hypothyroidism).

It should be noted that THs control cell growth and metabolism, so alteration of TH levels by PBDEs may induce neurotoxicity as THs play important roles in brain development during the developmental stages of the foetus (Kim et al., 2012; Lin et al, 2011; Voung et al., 2018). Several studies have reported inverse associations of prenatal PBDE exposures with childhood emotional control, attention, executive function and working memory (Eskenazi et al., 2013; Sagiv et al., 2015; Vuong et al., 2016; Vuong et al., 2018). Consequently, new-borns with higher prenatal exposure to PBDEs are more likely to suffer from neurodevelopment deficits. Further studies on the neurodevelopment effects of prenatal PBDE exposure in Uganda are warranted.

4. Conclusions

The present study is the first report on the ubiquity of BDE congeners in maternal placenta and cord blood samples in Uganda. The levels of PBDEs in the two compartments did not differ significantly and, in majority cases, the levels were generally lower and/or in the same range of data compared to those observed in other parts of the world. BDE-209 dominated the profiles in both matrices. In addition, observational comparison of the levels in the compartments showed that the extent of transplacental transport was generally higher for the highly brominated congeners than for the lower congeners, suggesting that the maternal-foetal TPT was not only through passive diffusion since this depends on molecular size. However, the sample sizes (N=30 for placentas and N=30 for cord blood) in this study are small, and do not provide

sufficient statistical power to allow generalisations and/or to detect the potentially subtle effects of low PBDE levels. A larger cross-sectional study with a larger number of participants is recommended. Secondly, other demographic characteristics such as maternal education level, occupation and gestational age-which are likely to affect PBDE accumulation-were not investigated due to the small sample sizes. In addition, literature on the levels of the pollutants in foods, as well as indoor and outdoor environments which might be affecting the variability of the levels in human samples in Uganda is not available. More studies are warranted.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Author contribution statement

Henry Matovu: Conceptualization, Methodology, Validation, Formal analysis, Investigation and Writing - Original Draft. **Patrick Ssebugere:** Conceptualization, Writing - Review and Editing, Supervision, Project administration, Funding acquisition. **Mika Sillanpää:** Writing - Review and Editing, Supervision, Funding acquisition.

Conflict of interest

The authors declare no conflict of interest.

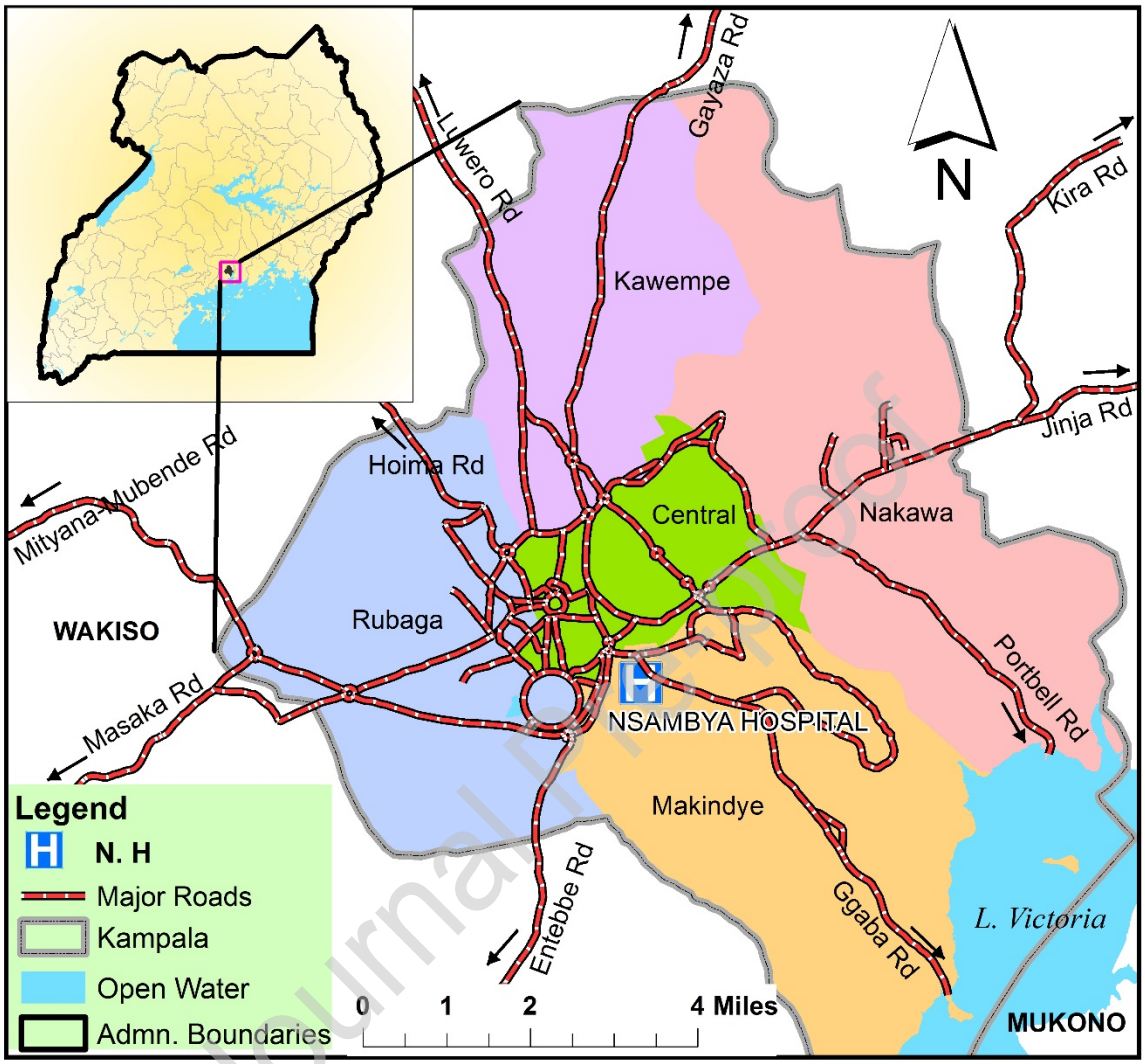
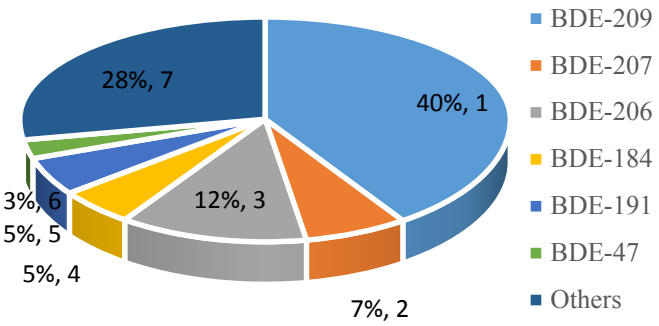
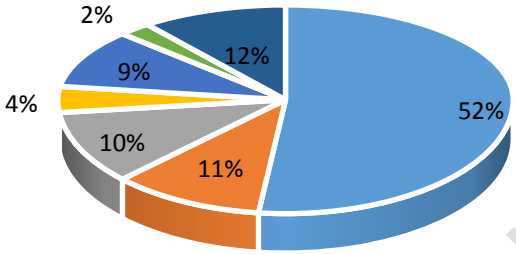


Fig. 1: Map of Kampala capital city from where samples were collected.



(a)



(b)

Fig. 2: Percentage contribution of the major BDE congeners to ∑PBDEs in **(a)** Placenta samples and **(b)** cord blood.

Highlights

- PBDEs were ubiquitous in placenta and cord blood samples of mothers from Uganda.
- No significant difference between PBDE levels in cord blood and placenta samples.
- BDE-209 was the dominant congener in both matrices.
- Fish and beef consumption did not significantly affect placental PBDE levels.
- Transplacental transfer was higher for deca- and nonaBDEs than for tri- pentaBDEs.

Table 1: Demographic characteristics of the study population (N = 30)

	Mean	*Median*	*Min-Max*
Maternal age (Years)	29.1	29	17-38
Prepregnancy BMI (kg/m^2)	29.2	27.8	22.4-41.8
Infant birth weight (kg)	3.39	3.45	1.9-4.6
		Frequency (persons)	
Infant sex	Male	12	
	Female	18	
Monthly household income (USD)	<136	5	
	136-274	8	
	>274	17	
Type of delivery	Normal	21	
	Caesarian	9	
Weekly consumption of beef/fish (persons (%))		*beef*	*fish*
	Never	2(6.7)	1(3.3)
	1-2 times	6(20)	15(50)
	3-5 times	17(56.7)	10(33.3)
	>5 times	5(16.7)	4(13.3)

Table 2: Levels of PBDEs (ng g^{-1} lw) in cord blood and placenta samples of mothers from Uganda.

	Umbilical cord blood (N=30)				**Maternal placenta (N=30)**			
Mean %lipid	0.54±0.36				0.83±0.41			
Congener	% > LOD	Median	Min	Max	% > LOD	Median	Min	Max
BDE-17	3.3		bdl	0.38	53.3	0.2	bdl	0.31
BDE-28	83.3	0.1	bdl	0.38	6.67		bdl	0.27
BDE-47	50	0.03	bdl	3.42	83.3	0.25	bdl	0.95
BDE-49	0.0				0.0			
BDE-66	0.0				10		bdl	0.27
BDE-71	0.0				6.67		bdl	0.17
BDE-77	0.0				3.3		bdl	0.11
BDE-85	0.0				3.3		bdl	0.51
BDE-99	23.3		bdl	0.75	13.3		bdl	0.51
BDE-100	0.0				0.0			
BDE-119	0.0				0.0			
BDE-126	0.0				0.0			
BDE-138	3.3		bdl	0.3	63.3	0.6	bdl	0.76
BDE-153	80	0.3	0.22	1.13	76.7	0.63	bdl	1.0

BDE-154	20		bdl	0.49	10		bdl	0.45
BDE-156	6.7		bdl	0.57	10		bdl	0.63
BDE-183	100	0.5	0.31	1.89	0.0		bdl	Bdl
BDE-184	70	0.41	bdl	1.4	33.3		bdl	0.28
BDE-191	66.7	0.46	bdl	11.4	46.7		bdl	1.27
BDE-196	3.3		bdl	3.4	46.7		bdl	1.81
BDE-197	3.3		bdl	3.78	46.7		bdl	2.54
BDE-206	50	0.1	bdl	5.8	23.2		bdl	7.1
BDE-207	56.7	0.4	bdl	7.54	20		bdl	5.9
BDE-209	63.3	7.95	bdl	18.3	46.7		bdl	10.2
$\sum_{24}$PBDEs	**100**	**11.9**	**1.65**	**34.5**	**100**	**7.76**	**0.25**	**30.9**

N- number of samples; bdl-below detectable limit; % > LOD - percentage of samples with congener level above the detection limit

Table 3: Median levels of PBDE congeners (ng g^{-1} lw) measured in human placenta tissues from different regions around the world

			Major BDE congener								∑PBDE			
Country	N	Year of sampling	28	47	99	100	153	154	183	197	209	Median	Min-Max	n	Ref
Uganda	30	2018	bdl	0.25	bdl	bdl	0.63	bdl	bdl	bdl	bdl	7.76	0.25-30.9	24	This study
Tanzania	45	2012		2.51	3.74							7.87	1.17-347	11	Müller et al. (2019)
South Korea	108	2011	0.12	0.6	0.25	0.09	0.23				9.59	11.7	1.21-427	24	Jeong et al. (2018)
South China	30	2012	0.44	6.73	0.89	bdl	0.64	0.47	0.45	0.39	bdl	12.7	4.32-42	17	Chen et al. (2014)
Giuyu, China	69	2012	11.7	1.61	0.32	0.14	3.17	0.34	2.2		3.3	32.3	0.89-517	8	Xu et al. (2015)
Haojiang,	82	2012	0.45	0.39	0.06	0.06	0.49	0.1	0.35		2.08	5.13	0.66-	8	Xu et al.

China												196		(2015)
												nd-		Ma et al.
China	130	2005-2007		0.22	0.097	0.011	0.1	bdl			0.54	11.1	6	(2012)
												1.5-		Bi et al.
China	21	n/a	0.63	1.4	0.47	0.22	0.8	0.12	0.2		3.9	12	7	(2006)
												3.37-		Zhao et al.
China	65	n/a	0.38	0.65	0.18	0.12	1.15	0.07	0.26	1.45	2.64	7	26.7	9	(2013)
														Takasuga et
Japan	10	2009-2011	0.013	0.09	0.027	0.02	0.065			0.049	0.32	n/a	n/a	9	al. (2006)
Durham,													0.54-		Leonetti et
NC, USA	102	2010-2011		5.05	1.95	1.65	2.36	0.74			2.64	16.1	528	6	al. (2014)
															Leino at al.
Finland	130	2004-2005	0.04	0.39		0.08	0.19	<.03	<0.16		<0.92	1.04	n/a	16	(2013)
													0.51-		Frederiksen
Denmark	50	2007	<0.03	0.32	0.23	0.066	0.35	0.09	<0.1		1.14	2.31	17.1		et al. (2009)
Spain	50	2004-2008	bdl	bdl	bdl		0.37	bdl				2.3		14	Vizcaino et

	al. (2014)

N-number of samples; n-number of congeners analysed; bdl-below detection limit; n/a- not analysed

Table 4: Median levels (ng g^{-1} lw) of PBDEs in cord blood samples from different regions around the world

			Major BDE congener										∑PBDE			
Country	N	Sampling Year	28	47	99	100	153	154	183	196	197	209	median	min-max	n	Reference
Uganda	30	2018	0.1	0.03	bdl	bdl	0.3	bdl	0.5	bdl	bdl	7.95	11.9	1.65-34.5	24	This study
Spain	308	2004-8	bdl	bdl	bdl		bdl	bdl				n/a	5.4		14	Vizcaino et al. (2014)
Spain	174	2004-6		2.3	1.5		<0.23	<0.08				<1.20	9.6	nd-140	15	Vizcaino et al. (2011)
Denmark	40	2007	0.05	<0.07	<0.29	<0.27	0.51	<0.05				<2.40	0.9	0.21-54.3	12	Frederiksen et al. (2010)
France	90	2004-6	bdl		2.43	1.37	0.49	0.09	0.59	0.42	0.74	27.1				Antignac et al. (2009)
Sweden	10	2005-6	<0.14	3.4	<0.27	<0.57	2.4	0.15			0.88	4.7	4.7	1.2-26	13	Jakobsson et al. (2012)
China	80	2011-13		0.54			3.46	0.28				71.9	144		19	Zhao et al. (2016)
China	232	2010-12	2.05	3.71	6.7	2.63	2.19	bdl	bdl			n/a			8	Ding et al. (2015)
China	30	2012	0.1	3.82	0.35	bdl	0.57	0.45	bdl	1.29	bdl	bdl	9.73	1.02-71.3	17	Chen et al. (2014)
South Korea	118	2011		2.19	1.65	bdl	bdl	Bdl				n/a	6.57	1.92-11.6	19	Choi et al. (2014)

South Korea	21	2008	0.03	7.85	0.38	0.15	1.68	0.05		n/a	12	2.28-30.9	13	Kim et al. (2012)
South Korea	108	2007	0.35	6.12	2.08	0.8	3.49	0.54	2.04	n/a	8.23	nd-29.4	8	Kim et al. (2009)
Taiwan	54	2007-8	0.1	0.67	0.72	0.17	0.92	0.1	0.51	n/a	3.49	1.65-47.3	8	Lin et al. (2011)
USA	210	2001		11.2	3.2	1.4	0.7	0.6	0.6	n/a				Herbstman et al. (2010)
Canada	97	2004-8	5.93	50.5	17.9	6.79	5.55	3.11	3.88	n/a	100	51-1449	8	Foster et al. (2011)

N-number of samples; n-number of congeners analysed; bdl-below detection limit; n/a- not available