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Polybrominated diphenyl ethers in mothers' breast milk and associated health risk to nursing infants in Uganda

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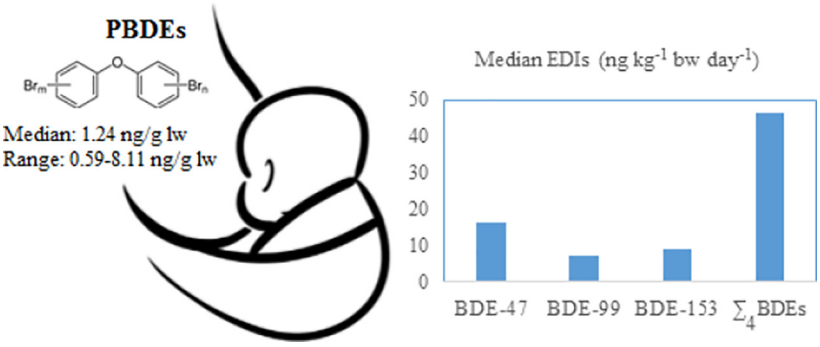
HIGHLIGHTS

- 12 PBDE congeners were detected in breast milk of mothers from Uganda.
- BDE-209 was the most predominant congener (contributed 37.1% to the ∑PBDEs).
- Fish consumption was associated with higher levels of BDE-47.
- EDIs were less than US EPA reference doses for BDE-47, -99 and -153.
- RQs were <1 in 96% samples indicating that the milk was fit for infant consumption.

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of this study was to investigate levels of polybrominated diphenyl ethers (PBDEs) in breast milk samples from healthy primiparous mothers who had lived in Kampala capital city (urban area) and Nakaseke district (a rural area) for the last five years. Fifty samples were collected between March and June 2018 and were extracted by dispersive solid-phase extraction (SPE). Clean-up was performed on an SPE column and analysis was done using gas chromatography–mass spectrometry. Total (∑) PBDEs (BDE 28, 47, 49, 66, 77, 99, 100,138,153, 154, 183 and 209) ranged from 0.59 to 8.11 ng/g lipid weight (lw). The levels of PBDEs in samples from Kampala capital city were significantly higher than those from Nakaseke ($p < 0.01$, Mann-Whitney U test). The most dominant congeners were BDE-209 and -47 (contributed 37.1% and 20.2%, respectively to ∑PBDEs), suggesting recent exposure of mothers to deca-and penta-BDE formulations. Fish and egg consumption, plastics/e-waste recycling and paint fumes were associated with higher levels of BDE-47, -153 and -99, respectively, implying that diet and occupation were possible sources of the pollutants. Estimated dietary intakes (ng kg^{-1} body weight day^{-1}) for BDE-47, -99 and -153 were below the US EPA reference doses for neurodevelopmental toxicity, suggesting minimal health risks to nursing infants who feed on the milk. Generally, the risk quotients for BDE-47, -99 and -153 were <1 in majority (96%) samples, indicating that the breast milk of mothers in Uganda was fit for human consumption.

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1. Introduction

Over the last two decades, most urban areas in Uganda have experienced rapid industrialisation and urbanisation. These developments, coupled with the importation of consumer goods such as old electrical and electronic waste (e-waste) in the name of "recycling" from developed countries, are creating new sources of pollutants (Asante et al., 2011; Robinson, 2009). Although Uganda passed regulations for managing e-waste (Ministry of ICT, 2016), poor recycling and disposal methods such as open burning and dumping at non-constructed or poorly constructed landfill sites are still being used and have resulted in increased pollution of environmental systems in most urban areas such as Kampala capital city (Arinaitwe et al., 2014). Some of the chemicals that are released from the aforementioned sources are polybrominated diphenyl ethers (PBDEs) and related chemicals.

PBDEs are compounds mainly used in household items such as electronics, fabrics, foam cushions, furnishings and paints because they slow down the rate of ignition and fire growth in petroleum-based polymers and resins (Bramwell et al., 2017; Zhang et al., 2016). The manufacture of products containing PBDEs has been banned and/or restricted in most countries in the world but they continue to be used in already manufactured products (Chao et al., 2010). It should be noted that PBDEs are physically blended in polymers and can thus leach out into the environment during production, use, disposal and recycling (Vuong et al., 2018). The compounds are characterised by being persistent and, can undergo volatilisation and long-range atmospheric transport, thus can be found in places far from their areas of use (Arinaitwe et al., 2014). They are lipophilic, so can bioaccumulate in fatty tissues of living organisms and biomagnify in the food web (Abballe et al., 2008; Fromme et al., 2016; Ni et al., 2013). As a result, the chemicals have been reported in a variety of fatty foods of animal origin such as eggs (Babalola and Adeyi, 2018; Huang et al., 2018; Polder et al., 2016) and fish (Schecter et al., 2006; Ssebugere et al., 2014; Voorspoels et al., 2007), as well as in human samples (Asante et al., 2011; Bjermo et al., 2017; Bramwell et al., 2014; Chen et al., 2014; Cui et al., 2012; Darnerud et al., 2011; Jakobsson et al., 2012; Mannetje et al., 2013; Müller et al., 2016; Müller et al., 2019).

The major pathways of the pollutants into human bodies include ingestion of contaminated food and ingestion and/or inhalation of contaminated dust (Fraser et al., 2009; Jones-Otazo et al., 2005; Lee et al., 2013). Previous studies have reported that diet is the most significant source of exposure to lower BDE congeners (Domingo et al., 2008) while indoor dust is a significant source of higher congeners (Chao et al., 2014; Coakley et al., 2013; Schecter et al., 2005). Compared to adults, infants tend to have a higher exposure to PBDEs through dust ingestion due to their close proximity to the floor and frequent hand-to-mouth activities (Fromme et al., 2016; Stapleton et al., 2012). In terms of diet, nursing mothers are specifically susceptible to pollutant exposure because they are obliged to feed on a diet rich in animal protein including fish, milk and eggs, during pregnancy or breast feeding (WHO, 2019). In this respect, mothers can transfer these undesirable chemicals to the infants either prenatally or postnatally.

The pollutants have been implicated in a broad range of adverse effects such as endocrine disruption (Costa and Giordano, 2007; Schreiber et al., 2010). *In utero* exposure to PBDEs has been reported to have inverse associations with birth outcomes such as birth weight, birth length, head circumference, chest circumference and body mass index of infants (Chao et al., 2007; Lignell et al., 2013; Lopez-Espinosa et al., 2015). In addition, prenatal and infant exposure to PBDEs leads to neurodevelopmental deficits (Cowell et al., 2018; Costa and Giordano, 2007; Ding et al., 2015; Eskenazi et al., 2013; Sagiv et al., 2015) and increases the risk of cryptorchidism in male infants (Goodyer et al., 2017). As a result of the toxic effects, the compounds have been listed as priority persistent organic pollutants (POPs) for elimination by the Stockholm Convention (Stockholm Convention, 2019). Uganda acceded to the convention in 2004 and is required to have a National Implementation Plan for the Convention.

Owing to the growing level of industrialisation in Uganda, we hypothesised that industrial activities and e-waste recycling were exposing the mothers especially those in Kampala to PBDEs, which could have deleterious effects on their breast feeding infants. However, a survey of literature showed no information about the levels of PBDEs in breast milk of mothers from Uganda and their association with maternal demographic characteristics. Furthermore, no data was available about the health risks posed to nursing infants through the consumption of the contaminated milk. Whether dietary intake was a significant route for maternal exposure to PBDEs could not be justified. Therefore, the aim of this study was to assess the levels and possible determinants of PBDEs in human milk in Uganda, and to estimate infant dietary intakes of PBDEs through breastfeeding.

2. Methods and materials

2.1. Study population and sample collection

Participants were healthy pregnant women who were identified during routine prenatal obstetrics checks at St Francis Hospital Nsambya, Uganda. Recruitment was based on the willingness of the mothers to participate in the study and their residence time in Kampala. Kampala was chosen because it is the most industrialised and urbanised city in Uganda. The city harbours a population of over 1.5 million people according to the 2014 national census (Uganda Bureau of Statistics, 2016). Samples were collected between April and June 2018, from fifty two healthy and primiparous mothers (van den Berg et al., 2017). However, two samples were excluded, because one mother voluntarily opted out while for the other, the questionnaire about maternal and infant characteristics was misplaced. Of the fifty mothers left, 25 had lived in Kampala capital city (an urban area) for the last five years. Furthermore, 25 mothers who had lived in the rural areas of Nakaseke district for the last five years were taken as control. Nakaseke district is 60 km from Kampala city (Fig. 1) and the major activity in the district is subsistence farming.

At least 15 ml of breast milk was collected from each donor mother by manual expression with the help of a physician between the 2nd and 8th day of postpartum. The samples were directly collected into solvent cleaned polypropylene bottles and labelled using a permanent marker. The sample bottles were transferred to UN boxes packed with dry ice and shipped to the National Institute for Health and Welfare, Finland where they were frozen at −20 °C to avoid microbial decay before extraction.

2.2. Ethical considerations

Ethical approval of the study was granted by the Research and Ethics Committee of the Uganda National Council for Science and Technology and St Francis Hospital Nsambya, Uganda. All donor mothers signed an informed consent form and completed a questionnaire about their demographic characteristics and those of their infants (Table 1). The questionnaire was modified from the WHO guidelines (WHO, 2007). The details of the consent form and questionnaires, as well as the aim of the project were clearly explained to the mothers before participation. All information from the donor mothers and their children was kept confidential.

2.3. Chemicals and reagents

Chemical standards included 12 PBDE congeners (IUPAC congener numbers 28, 47, 66, 77, 99, 100, 138, 153, 154, 183, 197 and 209) and internal standards (^{13}C-labelled BDE-28, ^{13}C-labelled BDE-153, and ^{13}C-labelled BDE-197). Chemical standards used in the present study were purchased from Cambridge Isotope Laboratories (Andover, MA, USA),

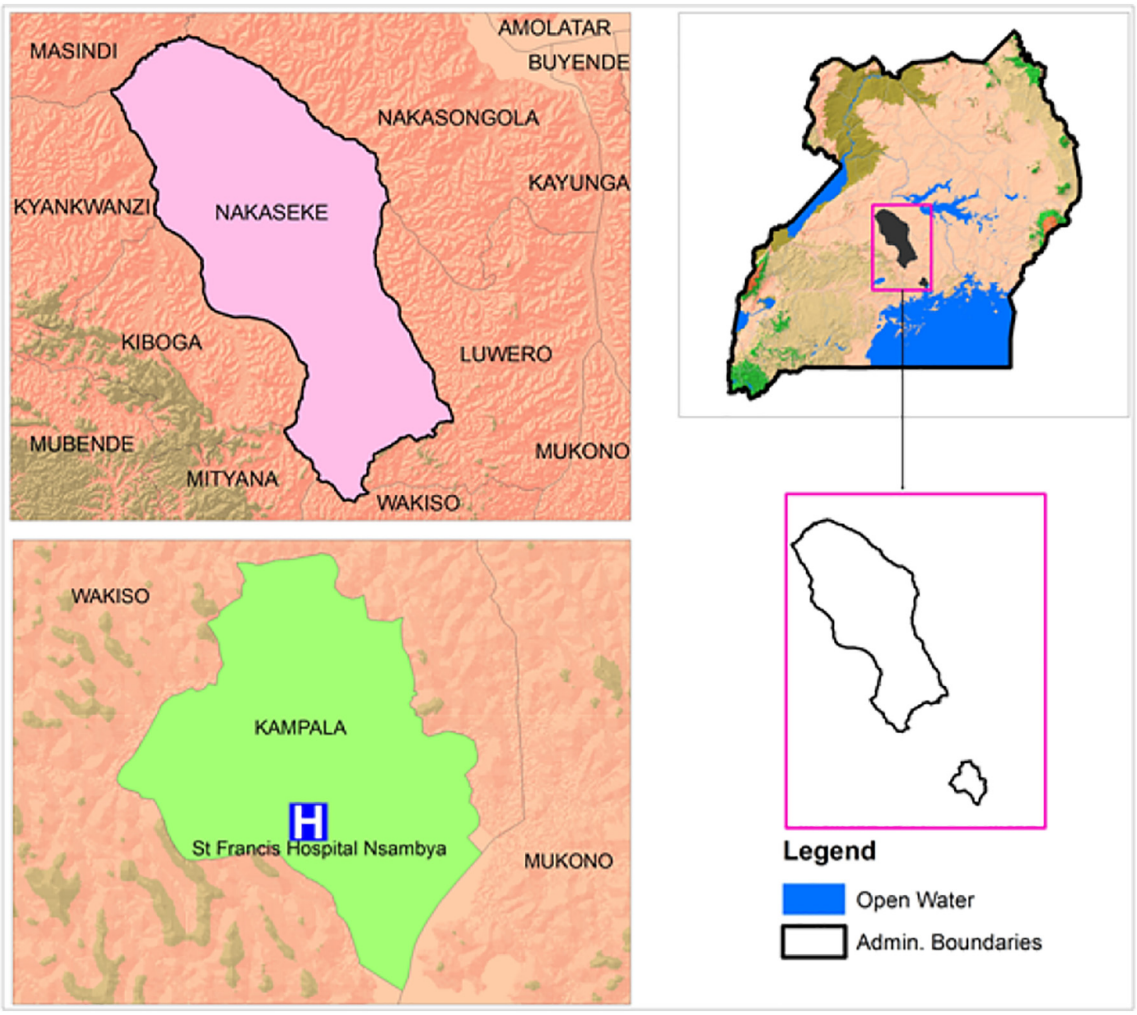

Fig. 1. Map of Uganda showing the locations of Kampala capital city and Nakaseke district.

Table 1
Maternal/infant characteristics of the participants.

Maternal/infant characteristics	Nakaseke ($N = 25$)		Kampala (N = 25)		All ($N = 50$)	
	Mean (Median)	Min-Max	Mean (Median)	Min-Max	Mean (Median)	Min-max
Maternal age (years)	29.5(29)	22–40	29.4(29)	22–44	29.5(29)	22–44
Infant birth weight (kg)	3.32(3.29)	2.6–3.9	3.31(3.4)	2.45–3.9	3.33(3.37)	2.45–3.9
Maternal pre-pregnancy BMI (kg/m^2)	29.1(29.1)	20.6–42.8	30.6(29.3)	22.1–46.7	29.8(29.1)	20.6–46.7
BMI ranges (persons)						
18.5–<25	4		4		8	
25–<30	11		11		22	
30–<35	7		5		12	
35–<40	2		2		4	
>40	1		3		4	
Reported exposure to pollutants (persons)	Never	Sometimes	Never	Sometimes	Never (%)	Sometimes (%)
Fumes from paints	15	8	5	20	22(44)	28(56)
Burning plastics and/or e-waste recycling	21	4	7	18	28(56)	22(44)
In-door spraying of pesticides	15	10	21	4	36(72)	14(28)
Oil fumes	11	14	18	7	29(58)	21(42)
Fumes from coal	20	5	0	25	20(40)	30(60)
Reported weekly food consumption (persons)	Never consumes	Consumes at least once	Never consumes	Consumes at least once	Never consumes (%)	Consumes at least once (%)
Eggs	7	18	1	24	8(16)	42(84)
Fish	6	19	4	21	10(20)	40(80)
Beef	4	21	0	25	4(8)	46(92)
Milk	2	23	2	23	4(8)	46(92)

Accustandard (New Haven, CT, USA) and Wellington Laboratories (Guelph, ON, Canada). Analytical grade *n*-hexane, sodium sulfate and silica gel 60 (Merck, Darmstadt, Germany), high purity ethanol (Altia, Rajamäki, Finland), dichloromethane (J.T. Baker, Deventer, the Netherlands) and silver nitrate (VWR International, Leuven, Belgium) were used. Silver nitrate-impregnated silica (10%, w/w) was prepared by dissolving 10 g of solid silver nitrate in 40 ml of ultrapure water and mixing with 90 g of silica gel at 2500 rpm for 30 min using a mechanical shaker (Heidolph, Schwabach, Germany). The mixture was activated for 2 h at 150 °C in an oven. All preparations were performed in the dark. Anhydrous sodium sulfate was activated at 500 °C for 2 h while silica-gel was activated at 120 °C for 48 h.

2.4. Sample extraction, clean-up and analysis

2.4.1. Extraction

An extraction method described by Koponen et al. (2013) was used with minor modifications. Briefly, a milk sample (13 ml) was carefully transferred into an extraction tube and spiked with 400 pg of each ^{13}C-labelled congener in 100 μl of toluene. Ethanol (250 μl) was added and the mixture vortexed for 4 min at 1800 rpm with Multi-Tube Vortexer (Henry Troemner, West Deptford, NJ, USA) to precipitate the proteins and equilibrate the internal standards. Activated silica-gel (5 g) was added and the PBDEs were extracted with a dichloromethane/*n*-hexane mixture (10 ml, 1:4 v/v) by vortexing for 4 min at 1800 rpm. The upper dichloromethane/*n*-hexane layer was loaded onto solid-phase extraction (SPE) glass column for clean-up. Extraction of the lower semi-solid layer was repeated twice and the extract was also loaded onto the column.

2.4.2. Clean-up

The SPE column was packed from bottom to top with 2 g of 44% silica gel-sulfuric acid, 4 g of 10% impregnated silica gel-silver nitrate and 2 g of anhydrous sodium sulfate. The column was conditioned with 5 ml of dichloromethane/*n*-hexane (1:4 v/v) before use. The extract was added to the conditioned column and eluted with 4 ml of dichloromethane/*n*-hexane (1:4 v/v). The eluate was concentrated to 30 μl with a gentle flow of nitrogen, transferred to an autosampler vial and then kept at −20 °C before instrumental analysis.

2.4.3. Lipid content determination

The lipid content of each sample was determined gravimetrically from a portion of the sample as described by Jaraczewska et al. (2006). Briefly, an aliquot of breast milk (2 ml) was extracted with a mixture of *n*-hexane: Ethanol (1:1, v/v). The organic layer was passed through a 3 ml polypropylene cartridge filled with anhydrous Na_2SO_4. The resulting filtrate was then evaporated to dryness using a stream of nitrogen and the lipid weight determined.

2.4.4. Instrumental analysis

The quantification of analytes was performed by using an Agilent 78904 gas chromatograph (GC) equipped with an Agilent 7010 triple quadrupole mass spectrometer (MS). Chromatographic separation was achieved using a DB-5MS UI column (60 m × 0.25 mm internal diameter × 0.25 μm film thickness). For BDE congeners 138, 153, 183 and 209, a ZB-5MS Plus-column (6 m × 0.18 mm internal diameter × 0.18 μm film thickness) was used. The MS was operated in electron capture negative ionisation (ECNI) and selected ion monitoring modes. The GC/MS operating conditions were set as described elsewhere (Darnerud et al., 2015).

2.5. Quality assurance/quality control

Quality assurance/quality control procedures included regular procedural and spiked blanks. A procedural blank was analysed simultaneously with every batch of ten samples to check for interferences and background contamination from solvents and glassware. Procedural blanks were consistent (RSD <15%) and the mean value was calculated for each analyte and subtracted from the values in the samples. To check for accuracy of the method, a low-fat sample of cow's milk with a known fat content was purchased and analysed. Two spiked cows' milk samples were also included in the analyses and the results were 91 and 98% of the spiked values. The limit of detection (LOD) for each analyte was estimated as three times the signal to baseline noise. The LODs ranged from 0.01 to 0.5 ng/g lw. Recovery tests were done using ^{13}C-labelled BDE standards. In all cases, the recoveries for the surrogates varied from 69 to 110%. Since the recoveries were within the acceptable range of 50–120%, the data was not corrected for recovery.

2.6. Estimation of dietary intake and health risk assessment

The estimated daily dietary intake (EDI) of infants through consumption of breast milk contaminated with the polybrominated diphenyl ethers was calculated using the formula:

$$EDI = C_i \times F_w \times (d/w_i)$$

where; EDI is estimated daily dietary intake (ng kg^{-1} body weight day^{-1}), C_i is the sample concentration of the congener in ng/g lw, F_w is the lipid content in the sample, d is the infant's daily milk consumption and w_i is the weight (kg) of the infant. To allow comparisons be made with other studies, the same assumptions as described by Van Oostdam et al. (1999) were used *i.e.*, a baby of 5 kg is assumed to take 700 g of milk per day. The health risk posed to infants was assessed using hazard quotients (HQs). HQ was calculated as a ratio of the calculated EDI of the congener to its corresponding maximum acceptable oral reference dose (Rfd) for humans. The Rfd represents an estimate of the oral daily dose at which no adverse effects as a result of exposure to pollutants is expected (Lyche et al., 2015). However, it should be noted that infants are more vulnerable to chemical exposure due to their poor xenophobic metabolic capacity (Müller et al., 2016) and could therefore have lower RfDs than for adults. The human RfDs for neurodevelopmental toxicity for BDE -47, -99 and -153 are 0.1, 0.1 and 0.2 μg/kg/day respectively (Lyche et al., 2015), while RfD of 0.1 μg/kg/day may be applied for the sum of all PBDEs between 47 and 183 (Linares et al., 2015). Normally, a HQ >1 suggests potential risk while a value <1 indicates no adverse effects as a result of exposure to contaminants (Hassine et al., 2015).

2.7. Statistical analysis

To aid comparison with other studies, the concentrations of analytes were lipid-based. During statistical analysis, analytes below the LOD were estimated as LOD/√2 and only congeners with a detection frequency of >60% were included in correlation analyses. The levels of PBDEs were not normally distributed hence, statistical differences between levels of the pollutants in the two study areas were examined using the Mann-Whitney *U* test. Further, the lipid-based levels of the different congeners were log-transformed before regression analyses. The normality of the log-transformed data was confirmed using the Kolmogorov-Smirnov test. Pearson correlation analysis was performed to examine the relationships between the log-transformed levels of the analytes and maternal exposure factors. Univariate regression relationships were first determined between the log transformed levels of the congeners and the covariates (fumes from paint, fumes from coal burning, fumes from e-waste recycling, exposure to pesticides and dietary habits). Covariates with a *p*-value <0.2 were then included in multiple regression models. Relationships amongst congener levels, as well as their relationships to maternal age, pre-pregnancy body mass index (BMI) and infant birth weight were investigated using Spearman's rank correlation. All statistical analyses were performed using the

SPSS 21.0 for Windows (Chicago, IL, USA) and in all cases, differences were considered significant when the exact p value was <0.05.

3. Results and discussion

3.1. Maternal characteristics

Donor mothers' demographic characteristics such as age, body mass index (BMI) before pregnancy, reported exposure factors and dietary habits are presented in Table 1. The mean age and pre-pregnancy BMI were 29.4 ± 4.78 years and 29.8 ± 6.02 kg/m^2, respectively. It was observed that, based on the WHO classification, 44% of the donor mothers were overweight (BMI, 25–<30 kg/m^2) whereas 40% of them were obese (BMI 30 kg/m^2 or higher). Pre-pregnancy BMI was significantly positively associated with infant birth weight (Spearman's rho, $\rho = 0.469$, $p = 0.014$) whereas no significant correlation was observed between BMI and maternal age ($\rho = 0.220$, $p = 0.125$). The study noted that mothers had mixed diets; 92%, 84%, 80% and 92% of the donor mothers consumed beef, eggs, fish and milk, respectively at least once a week.

3.2. Levels and congener profiles of PBDEs

The concentrations of 12 PBDE congeners in breast milk samples collected from Nakaseke and Kampala capital city are presented in Table 2. Total ($\sum$) concentrations of PBDEs varied from 0.59 to 8.11 ng/g lw (median 1.24 ng/g lw). The levels were in the same range of data as that reported in South Africa (median 1.3 ng/g lw) (Darnerud et al., 2011), Greece (1.5 ng/g lw) (Dimitriadou et al., 2016) and Germany (1.5 ng/g lw) (Hoopmann et al., 2012). However, the concentrations were lower than those reported in other African countries such Tanzania (19.8 ng/g lw) (Müller et al., 2016), Ghana (4.5 ng/g lw) (4.5 ng/g lw) (Asante et al., 2011) and Tunisia (9.8 ng/g lw) (Hassine et al., 2012), as well as those reported in developed countries such as UK (5.59 ng/g lw) (Bramwell et al., 2014), USA (19.6 ng/g lw) (Johnson-Restrepo et al., 2007) and Canada (19.9 ng/g lw) (Ryan and Rawn, 2014). Table 3 further compares the median levels of the different BDE congeners around the world. For standardization purposes, WHO recommends sampling time for human breast milk of at least 2 weeks of postpartum. Consequently, measurement of PBDEs in colostrum is not usually done. However, in our study collection of samples after 2 weeks of postpartum was not possible because it is extremely difficult to find mothers after they have left the hospitals. Besides, a study by Yu et al. (2007) compared levels of organohalogen POPs in colostrum and mature milk and reported no significant differences in the levels between the two sampling events. Since PBDEs are structurally similar to PCBs and organohalogen pesticides used in Yu et al. (2007), comparison between levels of PBDEs in colostrum in the present study and those in mature milk for other studies may be valid.

In this study, the concentrations of PBDEs in mothers from Kampala were significantly higher than those from Nakaseke ($p < 0.01$, Mann-Whitney U test). The difference indicates that mothers in urban areas such as Kampala are exposed to more sources of PBDEs (such as electronics and carpets) than those in rural areas. Several studies have reported that indoor dust from computers, domestic carpets and mattresses contain significant amounts of PBDEs and/or related compounds (Schecter et al., 2005; Coakley et al., 2013). In this study it was not possible to include this information. Hence, studies to investigate and compare in-door exposure in urban and rural areas need to be carried out in Uganda.

BDE-209 was the most predominant congener (contributed 37.1% to the $\sum$PBDEs), followed by BDE-47 (20.2%), BDE-153 (11.2%) and BDE-77 (8.5%) (Fig. 2). The distribution patterns of the congeners did not differ significantly between the sampling areas, suggesting that the mothers are exposed to PBDEs through similar sources. The trend observed in our study is in contrast to several other studies in which BDE-47 or BDE-153 is the predominant congener in human samples and wildlife (Brasseur et al., 2014; Chen et al., 2014; Cowell et al., 2018; Dimitriadou et al., 2016; Kang et al., 2010; Kim et al., 2012; Ryan and Rawn, 2014; Thomsen et al., 2010). A recent study in neighbouring Tanzania reported the predominance of BDE-99 in breast milk samples (Müller et al., 2016); whereas BDE-183 was the most dominant congener in breast milk samples from Tunisia and South Africa (Darnerud et al., 2011; Hassine et al., 2012). However, the predominance of BDE-209 has been reported in human serum samples from Sweden and Germany (Darnerud et al., 2015; Fromme et al., 2016) and breast milk samples in Belgium (Croes et al., 2012). These differences in the congener profiles suggest that humans are exposed to different BDE mixtures, which vary within regions or countries.

It should be noted that penta- and octa-BDE formulations were banned in Europe, United States and elsewhere in the world in 2005 while deca-BDE formulations were in use until 2013 (Darnerud et al., 2015; Guo et al., 2016; Stockholm Convention, 2019). Therefore, the distribution profiles of BDE congeners in human samples might have changed in recent decades as a result of the ban. BDE-209 has a short half-life (15 days) in humans (Darnerud et al., 2015; Thuresson et al., 2005), so its predominance in our samples suggests recent and ongoing exposure to the commercial deca-BDE formulation in which it is a major component. Predominance of BDE-209 could also be attributed to the declining levels of BDE congeners 47, 99, 100 and 153 as reported in recent studies (Darnerud et al., 2015; Guo et al., 2016). Increased exposure to BDE-209 raises health concerns since its breakdown may

Table 2
Levels (ng/g lw) of PBDE congeners in breast milk samples collected from Nakaseke and Kampala, Uganda.

BDE congener	Nakaseke (N = 25)				Kampala (N = 25)				All samples (N = 50)			
									Mean lipid % (1.22 ± 0.80)			
	Median	Mean	Range	n > LOD	Median	Mean	Range	n > LOD	Median	Mean	Range	n (%)[a]
BDE-28	<0.01	<0.01	–	0	<0.01	0.03	<0.01–0.3	12	<0.01	0.02	<0.01–0.3	6 (12)
BDE-47	0.14	0.21	<0.01–0.7	20	0.5	0.83	<0.04–3.21	23	0.21	0.52	<0.04–3.21	43 (86)
BDE-49	<0.01	<0.01	–	0	<0.01	0.09	<0.01–0.8	9	<0.01	0.05	<0.01–0.8	9 (18)
BDE-66	<0.01	<0.01	–	0	0.01	0.04	<0.01–0.3	9	0.09	0.02	<0.01–0.3	9 (18)
BDE-77	0.15	0.12	<0.01–0.23	20	0.07	0.13	<0.01–0.94	21	0.1	0.13	<0.01–0.94	41 (82)
BDE-99	0.06	0.06	0.03–0.08	18	0.05	0.15	<0.03–0.91	20	0.05	0.11	<0.03–0.91	38 (76)
BDE-100	<0.01	<0.01	–	0	<0.01	0.13	<0.01–0.92	9	<0.01	0.07	<0.01–0.92	9 (18)
BDE-138	<0.01	<0.01	–	0	<0.01	0.04	<0.01–0.32	6	<0.01	0.03	<0.01–0.32	6 (12)
BDE-153	0.09	0.11	0.01–0.22	21	0.17	0.37	<0.01–1.93	23	0.13	0.24	<0.01–1.93	44 (88)
BDE-154	<0.01	0.05	<0.01–0.21	9	0.05	0.26	<0.01–1.21	15	<0.02	0.15	<0.01–1.21	24 (48)
BDE-183	<0.03	<0.03	–	0	<0.03	0.15	<0.03–1.33	8	<0.03	0.09	<0.03–1.33	8 (16)
BDE-209	<0.5	<0.5	<0.5–1.42	5	0.72	0.92	<0.5–2.88	18	<0.5	0.69	<0.5–2.88	23 (46)
$\sum_{12}$PBDE	1.0	1.05	0.59–2.23		2.72	3.13	0.91–8.11		1.24	2.09	0.59–8.11	

[a] Number and percentage of samples with levels >LOD.

Table 3
Comparison of median levels (ng/g lw) of major BDE congeners in breast milk samples around the world.

Area	Sampling year	N	BDE congener										Reference
			28	47	66	99	100	138	153	154	183	209	
Africa													
Kampala and Nakaseke, Uganda	2018	50	<0.01	0.21	0.09	0.05	<0.01	<0.01	0.13	<0.01	<0.03	<0.5	This study
Arusha, Tanzania	2012	95		5.3		8.9	2.1		1.8				Müller et al. (2016)
Limpopo Province, South Africa	2004	28	0.06	0.3	0.06	0.06	0.06		0.38	0.06	0.32		Darnerud et al. (2011)
Accra, Ghana	2009	16	0.08	1.7		0.32	0.34		0.35	bdl	bdl	0.55	Asante et al. (2011)
Kumasi, Ghana	2009	14	0.07	1.7		0.32	0.25		0.22	bdl	bdl	0.39	Asante et al. (2011)
Tamale, Ghana	2009	12	0.04	0.49		0.05	0.07		bdl	bdl	bdl	0.95	Asante et al. (2011)
Bizarte, Tunisia	2010	36	0.56	2.1	0.19	1.08	1.48	bdl	1.51	0.67	2.03		Hassine et al. (2012)
Asia													
China	2012	30	1.11	3.84		0.62	0.19	1.12	1.65	0.47	1.18	bdl	Chen et al. (2014)
Philippines	2008	30	0.12	0.94		0.22	0.19		0.4	0.07	0.02	0.87	Malarvannan et al. (2013)
Shanghai, China	2006–2007	48	0.88	0.99		1.39	0.97		2.17	1.15	1.41		Cui et al. (2012)
Vietnam	2007–2008	20	0.04	0.19		0.02	0.02		0.14	0.05			Haraguchi et al. (2009)
China	2007–2008	25	0.43	0.89		0.07	0.08		0.38	0.05			Haraguchi et al. (2009)
Korea	2007–2008	29	0.14	2		0.33	0.28		0.86	0.13			Haraguchi et al. (2009)
Japan	2007–2008	60	0.07	0.64		0.12	0.11		0.39	0.16			Haraguchi et al. (2009)
Taiwan	2007–2008	32	0.09	0.52	0.01	0.15	0.17	0.01	0.86	0.07	0.1	0.36	Koh et al. (2010)
Europe													
Poland	2004	22	bdl	0.73		0.33	0.05		0.45		bdl		Jaraczewska et al. (2006)
Germany	2006–2009	2173	0.31			0.09	0.09		0.51				Hoopmann et al. (2012)
Greece	2004–2005	87	bdl	0.48		0.27	0.19		0.3	bdl	bdl		Dimitriadou et al. (2016)
Belgium	2009–2010	84	bdl	0.16		0.06	0.06		0.29	0.07	bdl	0.65	Croes et al. (2012)
UK	2011–2012	6	0.09	1.92	0.03	0.88	0.64	0.02	1.01	0.07	0.05	0.52	Bramwell et al. (2014)
Norway	2003–2010	393	0.09	0.99		0.27	0.25	0.04	0.45	0.04	0.06	0.32	Thomsen et al. (2010)
New Zealand													
New Zealand		33	0.18	2.14	0.03	0.56	0.5		0.52	0.04	0.04	0.19	Coakley et al. (2013)

N - number of samples; bdl-below detection limit.

result in lower brominated congeners and/or other products, which are more toxic than the parent compound (Darnerud et al., 2015). In addition, higher brominated congeners less readily transfer from blood to breast milk compared to the lower brominated congeners (Mannetje et al., 2013; Thomsen et al., 2010). Therefore, the levels of BDE-209 in breast milk may underestimate the actual body burden of this compound, since serum levels may be higher than those in breast milk. A study into the levels of PBDEs in human blood samples in Uganda is warranted.

The second most predominant congener in our samples was BDE-47. This could be attributed to on-going exposure to the penta-BDE formulation through recycling of waste consumer products. PBDEs are used as flame retardants in thermoplastics such as those used for making electrical appliances. Therefore, mothers living near waste disposal sites or

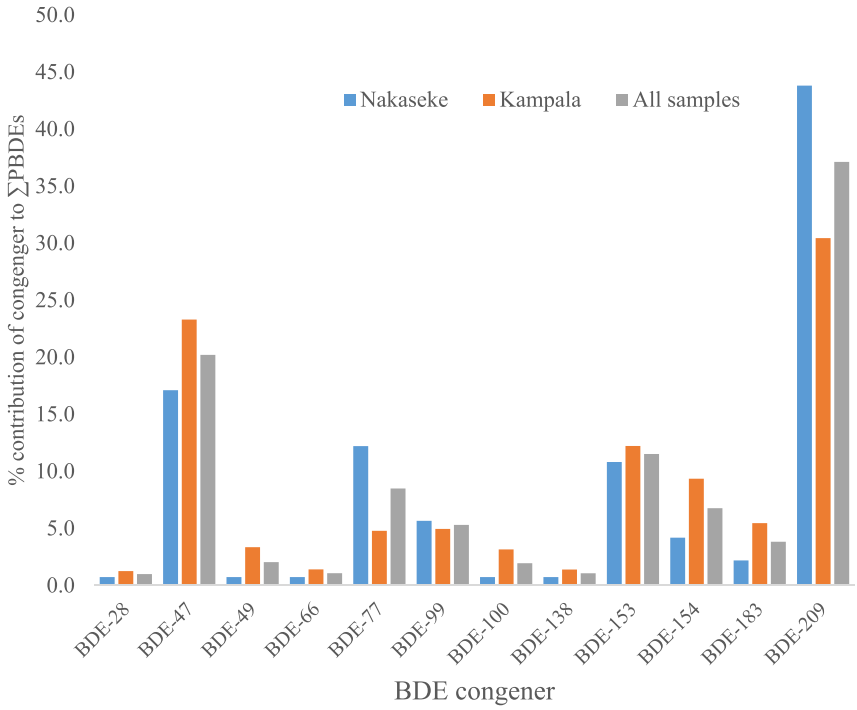

Fig. 2. Percentage contribution of the congeners to $\sum_{12}$PBDEs.

those involved in recycling may have higher PBDE levels (Malarvannan et al., 2013).

3.3. Association of PBDE levels with maternal age, BMI and infant birth weight

In the present study, maternal age had no significant association with the PBDE congeners (Table 4). The accumulation of persistent organic pollutants (POPs) with maternal age has frequently been reported for other compounds such as polychlorinated biphenyls (PCBs) but not with PBDEs (Dimitriadou et al., 2016; Herbstman et al., 2007). This may be attributed to the recent production and use of PBDEs, implying a higher on-going exposure to PBDEs compared to other legacy POPs such as PCBs whose production and use has long been prohibited (Müller et al., 2016). Herbstman et al. (2007) also suggested that lack of association of PBDEs levels with age may also be a result of a behavioural cohort effect in which younger women may have more contact with consumer products containing PBDEs or have a higher consumption of PBDE-containing diets. In addition, it could be due to lack of control for potential confounders such as parity, nursing history of the mothers and educational level which are capable of concealing the age correlation (Thomsen et al., 2010).

No significant association was observed between pre-pregnancy BMI and the levels of the congeners BDE-47, -77, -99 and -153 (Table 4). The observed lack of association was consistent with other studies on PBDEs (Müller et al., 2016). Furthermore, a study by Mannetje et al. (2013) showed that higher BMIs are associated with lower levels of POPs. The authors ascribed the trend to the dilution effect of body burdens of POPs during weight gain.

The present study also observed non-significant associations between the congeners BDE-47, -77, -99 and -153 with birth weight of the infants. Studies on the effect of prenatal PBDE exposure on infant birth outcomes have reported contrasting results. In Arusha, Tanzania, Müller et al. (2016) reported positive association of breast milk levels of BDE-47, -99, -100 and -153 with infant birth weight. Other studies (Chao et al., 2007; Lignell et al., 2013) reported inverse associations of PBDEs with birth outcomes. Mechanisms explaining associations of PBDE exposure with birth weight remain unclear but may involve effects on endocrine systems (Lignell et al., 2013). Epidemiological studies have reported the alteration of thyroid hormone levels by PBDEs which may affect foetal growth (Bowers et al., 2015; McIntyre et al., 2015).

3.4. Determinants of PBDE levels in breast milk

We further investigated the possible association between the maternal diet and exposure factors, and PBDE levels (Table 5). Dietary components such as milk, beef, fish and chicken eggs have been identified as major sources of PBDEs for humans (Babalola and Adeyi, 2018; Domingo et al., 2008; Thomsen et al., 2008). Fish and eggs consumption, exposure to fumes from paint and coal and plastic/e-waste recycling were used as covariates in the regression models while adjusting for maternal age and BMI as possible confounders. Regression analysis showed that mothers who consumed more fish on a weekly basis had higher levels of BDE-47 than those who consumed less fish. Furthermore, BDE-47 was positively correlated with exposure to fumes from paint and coal processing. Our results suggest that, in addition to occupational sources, mothers in Uganda are exposed to BDE-47 through fish consumption. A recent study Ssebugere et al. (2014) reported detectable levels of PBDEs (48.2–177 pg g^{-1} lw) in two of the major fish species consumed in Uganda. BDE-47 was the most dominant congener in the fish samples, consistent with other studies around the world (Ohta et al., 2002; Thomsen et al., 2008). Although levels reported by Ssebugere et al. were low, positive association between fish consumption and PBDE levels, such as that observed in this study, is likely to become more apparent over time owing to the bioaccumulation potential of PBDEs.

Regression analysis also showed that plastic/e-waste recycling was associated with higher levels of BDE-99 ($p = 0.003$), implying that mothers are likely to be occupationally and/or non-occupationally exposed to BDE-99 through recycling of products containing the penta-BDE formulation. The pentaBDE formulation, in which BDE-99 is a major component, has historically been used in polyurethane foams used in mattresses, cushioning and electrical wire and furniture coatings (Schecter et al., 2005). Based on our results, it could not be confirmed whether there could be additional indoor exposure to BDE-99 from products used at home such as mattresses, furniture and cushions as these have not been investigated in the present study. Hence, further studies are warranted.

BDE-153 was also positively associated with e-waste recycling, although the association was weak and not statistically significant. However, positive association of BDE-153 with eggs consumption ($p = 0.006$) was observed suggesting that eggs could be a significant dietary source of BDE-153. Since BDE-153 has a higher half-life (6.5 years) than BDEs-47 and -99 (1.8 and 2.9 years, respectively) (Geyer et al., 2004), it has a very high bioaccumulation potential in lipids, such as those in eggs. In addition, the accumulation of BDE-153 through metabolic step-wise meta debromination of BDE-209 is possible (Abdallah and Harrad, 2014; Roberts et al., 2011). In our study, BDE-153 was positively associated with BDE-209 ($\rho = 0.276$, $p = 0.048$) suggesting debromination of BDE-209 to BDE-153. A recent study by Polder et al. (2016) reported elevated levels of BDE-209 (0.2–311 ng/g lw) in eggs from free-range chicken in Tanzania. The authors attributed the levels to the scavenging behaviour of the birds exposing them to particle-bound contaminants (such as BDE-209), which could be debrominated to lower congeners (such as BDE-153). These congeners may find their way into the bodies of mothers through egg consumption. Whether significant levels of PBDEs occur in the eggs of chicken reared in Uganda needs further investigation.

Other factors listed in Table 1 were not significant predictors for the PBDE levels. Similarly, BDE-77 was not significantly associated with any of the listed factors. This suggests that there may be other factors affecting the variability of the contaminants in breast milk. For instance, Arinaitwe et al. (2014) reported significant levels of PBDEs (dominated by BDEs 47, 99 and 209) in air and precipitation samples from the

Table 4
Spearman's rho correlation coefficients (ρ) between PBDE congeners and maternal characteristics.

	logBDE-47	logBDE-77	logBDE-99	logBDE-153	log$\sum_4$BDEs
logBDE-47	1.00				
logBDE-77	−0.030 (0.835)	1.00			
logBDE-99	−0.04 (0.979)	−0.107 (0.459)	1.00		
logBDE-153	0.096 (0.506)	−0.421 (0.002)**	0.323 (0.022)**	1.00	
log$\sum_4$BDEs	0.849(0.000)**	0.047 (0.747)	0.071 (0.626)	0.297 (0.036)	1.00
Pre-pregnancy BMI	0.045 (0.759)	0.112 (0.437)	0.202 (0.160)	0.125 (0.388)	0.131 (0.364)
Maternal age	0.055 (0.707)	0.017 (0.905)	0.174 (0.226)	−0.097 (0.504)	0.040 (0.781)
Infant birth weight	−0.149 (0.458)	0.220 (0.270)	0.007(0.974)	0.016 (0.936)	0.105 (0.601)

Data is presented as ρ (p - value).
** Correlation is significant at $p < 0.05$ level.

Table 5
Results from Pearson regression analyses between the PBDEs and maternal exposure factors

Exposure factor	logBDE-47	logBDE-77	logBDE-99	logBDE-153	log$\sum_4$BDE
Fish consumption	0.424(0.000)**				0.552(0.000)**
Eggs consumption				0.398(0.006)**	0.203(0.052)
Milk consumption		-0.168(0.248)	0.154(0.249)		-0.086(0.408)
Paint fumes	0.422(0.000)**				0.174(0.100)
Fumes from coal processing	0.261(0.016)**				0.352(0.002)**
Plastic/e-waste recycling			0.405(0.003)**	0.168(0.080)	
Pesticides		-0.209(0.152)			0.003(0.974)
Adjusted R^2	*0.509*	*0.05*	*0.173*	*0.291*	*0.534*

Data is presented as standardized coefficient, β (*p*-value); **result is significant at 0.05 level

northern part of the Lake Victoria region. The authors attributed the levels to on-going exposure to penta-BDE formulations. Therefore, atmospheric deposition of the pollutants from point sources may be a significant contributor to the observed levels in breast milk. Further investigation of the PBDE levels in air, indoor and outdoor dust samples and other dietary components from Kampala city is warranted.

3.5. Infant dietary intake of PBDEs through breast milk

Breast-feeding is essential for the development of infants because milk contains immuno-protective constituents such as immuoglobulins, complement proteins, cytokines and some vitamins (Rawn et al., 2017). Mothers are therefore encouraged to feed their new-borns exclusively on breast milk for at least six months (WHO, 2018). However, exposure assessment studies have shown that POPs are capable of accumulating in the bodies of mothers and can be passed on to their infants during pregnancy and breastfeeding (Hassine et al., 2015). In this study, the estimated daily dietary intakes (EDIs) of BDE congeners 47, 99 and 153 and the sum of 4 congeners 47, 77, 99 and 153 ($\sum_4$BDEs) through breast milk were calculated. EDIs ranged from 1.6 to 69.9 ng kg^{-1} bw day^{-1} (median; 16.1 ng kg^{-1} bw day^{-1}) for BDE 47, 0.2 to 32.3 ng kg^{-1} bw day^{-1} (median; 7.3 ng kg^{-1} bw day^{-1}) for BDE 99, 0.6 to 51 ng kg^{-1} bw day^{-1} (median; 8.8 ng kg^{-1} bw day^{-1}) for BDE-153 and 10 to 149 ng kg^{-1} bw day^{-1} (median; 46.5 ng kg^{-1} bw day^{-1}) for $\sum_4$BDEs. Müller et al. (2016) reported median EDI values for BDE-47, -99 and -153 as 12.4, 20.1 and 4.1 ng kg^{-1} bw day^{-1}, respectively, in the breast milk of mothers from northern Tanzania. The values were in the same range of data as in the present study. EDIs for $\sum_4$BDEs in the present study were also lower than those reported in the breast milk samples of women from an e-waste recycling centre in China ($\sum_4$BDE$_s$; 15.8–243 ng kg^{-1} bw day^{-1}) (Li et al., 2017). Median EDIs were also lower than the US EPA reference doses (RfD) of the congeners (100 ng kg^{-1} bw day^{-1} for each of the BDEs 47, 99 and 153), except in two samples from Kampala, which exceeded the RfD (100 ng kg^{-1} bw day^{-1}) for $\sum_4$BDEs. In this study, risk quotients (RQs) were <1 in majority (96%) samples. The minority samples (4%) were from Kampala and had elevated levels of BDE-47; which could be a result of local sources of elevated exposure to the pentaBDE formulation. Overall, our results suggest that the breast milk in Uganda is not likely to cause risk to the nursing infants.

3.6. Strengths and limitations of the study

This is the first study to report the levels of PBDEs in human breast milk samples in Uganda. The study also explored the association of maternal PBDE levels with infant birth weight, maternal age, BMI and diet in the Uganda setting. A limitation of the study is that the number of individual participants recruited into the study ($n = 50$) is relatively small to allow generalisations be made. Secondly, in Uganda, limited data on the levels of PBDEs in other matrices such as food items and other human samples is available. This limited comparison of the observed levels in breast milk with those from the possible sources of the pollutants. Another limitation of the study was that exposure factors such as indoor and outdoor dust contamination, which have been proven to be important sources of the pollutants have not been considered in the present study. Furthermore, field blank samples were not included in our study. Since sampling was done manually; it is possible that our samples could have been contaminated by dust from the hospital equipment.

4. Conclusions

This study has determined baseline levels of 12 PBDE congeners in breast milk from Kampala capital city and Nakaseke district. The levels varied from 0.91 to 8.11 ng/g lw in mothers from Kampala, while those from the Nakaseke district ranged from 0.59 to 2.23 ng/g lw. The levels were in the same range of data, or lower than those of mothers in other countries in Africa, America and Europe. BDE-209 was the most predominant congener (contributed 37.1% to the ∑PBDEs), followed by BDE-47 (20.2%). Fish and egg consumption and occupational environments involving plastics/e-waste recycling, paint and coal fumes were important determinants of the levels. The levels of the pollutants showed no significant association with infant birth weight and maternal age. EDIs were less than the US EPA reference doses in 96% samples, so mothers in Uganda should be encouraged to continue breastfeeding their infants. Levels of other POPs such as PCBs and PCDD/Fs in breast milk, maternal and infant blood, diet and occupational environments need to be investigated to gain a full understanding of the pollutant burden in mothers and their potential transfer to nursing infants.

Declaration of Competing Interest

The authors declare no conflict of interest.

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