Emerging and legacy flame retardants in UK human milk and food suggest slow response to restrictions on use of PBDEs and HBCDD

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Abstract

The legacy flame retardants (LFRs) polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD), together with six emerging flame retardants (EFRs) were measured in United Kingdom (UK) human milk collected in 2010 (n=25) and 2014-15 (n=10). These data are the first report of the presence of EFRs in UK human milk. The most abundant EFR was β-tetrabromoethylcyclohexane (DBE-DBCH) (average = 2.5 ng/g lw; geometric mean = 1.5 ng/g lw), which is comparable to the concentrations of the most abundant LFRs i.e. BDE 47 and α-HBCDD at 2.8 and 2.1 ng/g lw, respectively (geometric mean = 2.1 and 1.7). The estimated average dietary intake of □EFRs by UK nursing infants was 18 ng/kg bw/day. EFRs were also measured in UK foodstuffs with β-DBE-DBCH again the predominant compound detected, accounting – on average – for 64.5±23.4% of □EFRs. Average estimated dietary intakes of ∑EFRs in the UK were 89 and 26 ng/day (1.3 and 2.6 ng /body weight/day) for adults and toddlers, respectively. Concentrations of Σtri-hexa BDEs in our UK food samples exceeded those reported in UK samples from the same food categories collected in 2003-04 and 2006. Despite this and our recent report elsewhere of significant temporal declines in concentrations of BDE 209 in UK indoor dust ($p < 0.05$) and HBCDDs in UK indoor dust and air ($p < 0.001$), no significant temporal differences ($p > 0.05$) were observed between concentrations of Σtri-hexa BDEs, BDE 209 and HBCDDs in human milk sampled in 2010 and those obtained in 2014-15. UK adult body burdens for EFRs were predicted via inhalation, diet and dust ingestion using a simple pharmacokinetic model. The predicted EFR body burdens compared well with observed concentrations in human milk.

Keywords	Emerging flame retardants; Brominated flame retardants; Human exposure; Human milk; Diet; Nursing infant.
Taxonomy	Exposure by Ingestion, Exposure Monitoring, Human Environmental Health Exposure, Environmental Health Exposure

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Emerging and legacy flame retardants in UK human milk and food suggest slow response to restrictions on use of PBDEs and HBCDD

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Abstract

The legacy flame retardants (LFRs) polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD), together with six emerging flame retardants (EFRs) were measured in United Kingdom (UK) human milk collected in 2010 (n=25) and 2014-15 (n=10). These data are the first report of the presence of EFRs in UK human milk. The most abundant EFR was β-tetrabromoethylcyclohexane (DBE-DBCH) (average = 2.5 ng/g lw; geometric mean = 1.5 ng/g lw), which is comparable to the concentrations of the most abundant LFRs i.e. BDE 47 and α-HBCDD at 2.8 and 2.1 ng/g lw, respectively (geometric mean = 2.1 and 1.7). The estimated average dietary intake of ΣEFRs by UK nursing infants was 18 ng/kg bw/day. EFRs were also measured in UK foodstuffs with β-DBE-DBCH again the predominant compound detected, accounting – on average – for 64.5±23.4% of ΣEFRs. Average estimated dietary intakes of ∑EFRs in the UK were 89 and 26 ng/day (1.3 and 2.6 ng /body weight/day) for adults and toddlers, respectively. Concentrations of Σtri-hexa BDEs in our UK food samples exceeded those reported in UK samples from the same food categories collected in 2003-04 and 2006. Despite this and our recent report elsewhere of significant temporal declines in concentrations of BDE 209 in UK indoor dust ($p < 0.05$) and HBCDDs in UK indoor dust and air ($p < 0.001$), no significant temporal differences ($p > 0.05$) were observed between concentrations of Σtri-hexa BDEs, BDE 209 and HBCDDs in human milk sampled in 2010 and those obtained in 2014-15. UK adult body burdens for EFRs were predicted via inhalation, diet and dust ingestion using a simple pharmacokinetic model. The predicted EFR body burdens compared well with observed concentrations in human milk.

Keywords: Emerging flame retardants; Brominated flame retardants; Human exposure; Human milk; Diet; Nursing infant.

Highlights:

- First investigation of EFRs in UK human milk.
- Estimated dietary exposures to EFRs comparable to dietary intakes of PBDEs.
- β-DBE-DBCH most abundant EFR in food and human milk.
- No significant change in PBDEs and HBCDD in human milk between 2010 and 2014-15
- Nursing infant exposure to EFRs exceeds adult and toddler dietary intakes.
- Observed body burdens of EFRs match closely those predicted via PK modelling

Introduction

Flame retardants have been incorporated within a wide range of consumer goods and materials to meet fire safety regulations. Due to their persistent, bioaccumulative and toxic properties, legacy flame retardants (LFRs) like polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDDs) were subject to various bans and restrictions under different jurisdictions. Penta- and Octa-BDE technical products were banned in Europe (including the UK) by 2004, and globally under the UNEP Stockholm Convention in 2009. Significant restrictions have been put on the Deca-BDE technical product in Europe since 2008, while HBCDD was listed under the Stockholm Convention in 2014 (European Court of Justice, 2008; Stockholm Convention, 2009; UNEP, 2014). This resulted in increasing concerns over the use of emerging flame retardants (EFRs) to replace the banned LFRs. Previous studies have highlighted substantially higher levels of BDE-209 in UK indoor dust compared to other European countries, which was mainly attributed to the extensive usage of Deca-BDE in upholstery fabrics and textiles in the UK (1,000-1,200 tonnes/year out of an estimated 1,500 tonnes/year in the EU for this application) to comply with the stringent UK Furniture and Furnishing Fire Safety Regulation 1988 (EU risk assessment report, 2002). While concentrations of LFRs have been decreasing in UK indoor air and dust over the last decade, those of EFRs have been reported to increase in the UK indoor environment (Tao et al., 2016). Moreover, the occurrence of EFRs has been widely documented recently in several environmental and biological matrices including indoor/outdoor air, indoor dust, soil, sediment, dietary items of animal origin, fish and birds (Cequier et al., 2014;Labunska et al., 2015; Li et al., 2015; Möller et al., 2011; Newton et al., 2015; Shi et al., 2009; Yang et al., 2012). This is of concern due to reports suggesting some EFRs (e.g. decabromodiphenyl ethane (DBDPE), 1,2-bis(2,4,6-

tribromophenoxy)ethane (BTBPE), EH-TBB and DBE-DBCH) are potentially persistent and bioaccumulative (He et al., 2012; Howard and Muir, 2010; Patisaul et al., 2013; Tomy et al., 2007). As a result, concentrations of EFRs in the human diet and tissues may increase in the future.

Given their similar structure to LFRs, EFRs may pose similar adverse effects to those displayed by LFRs. EFRs like DBE-DBCH, BTBPE, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)-tetrabromophthalate (BEH-TEBP) are capable of endocrine disruption and DNA damage (Bearr et al., 2010; Ezechiáš et al., 2012; Johnson et al., 2013; Khalafet al., 2009; Pradhan et al., 2013; Saunders et al., 2013). Despite such health concerns and evidence of exposure via indoor air and dust, very limited information on levels of EFRs in the human diet and human tissues exists to date. We are aware of only one UK and Irish diet study targeting hexabromobenzene (HBB), DBDPE and BTBPE, in which only BTBPE was detected in some UK food samples at concentrations ranging from 0.05-1.76 ng/g lw (Fernandes et al., 2010). Elsewhere, in a Swedish market basket study, EFRs were only detected in fish samples collected in 2010, with DBE-DBCH the predominant compound (Sahlström et al., 2015). In the same study, α-DBE-DBCH was found in two Swedish pooled human milk samples (average = 4 pg/g wet weight) collected in 2009-2010 (Sahlström et al., 2015). In the Sherbrooke region of Canada, Zhou et al. (2014) measured several EFRs including EH-TBB, BEH-TEBP, BTBPE, and DBDPE in paired human maternal serum (n = 102) and breast milk (n = 105) samples collected in 2008-2009. EH-TBB was detected in > 55% of both serum and milk samples, while BEH-TEBP, BTBPE, and DBDPE were also present but less frequently detected in both matrices (Zhou et al., 2014).

In the present study, 16 EFRs were investigated in 14 groups of composite food samples

95 covering meat, liver, oily fish, eggs and cheese to provide a preliminary estimate of UK dietary
96 exposure. Additionally, concentrations of 8 PBDEs and 3 HBCDD diastereomers were measured
97 in the same samples and compared with those reported in previous UK studies to evaluate the
98 impact of regulations and restrictions on these LFRs. Moreover, this study measures the
99 concentrations of EFRs in UK human milk for the first time, compares exposures of nursing
100 infants with that of adults and toddlers, and uses a simple one-compartment pharmacokinetic
101 model to forecast the body burdens of the studied EFRs and LFRs in UK adults and compare
102 these predicted burdens to those derived empirically from the analysed human milk samples.

Materials and methods

Chemicals and reagents

Solvents used were all of HPLC analytical grade (Fisher Scientific, Loughborough, UK). Standards of BDEs 28, 47, 99, 100, 153, 154, 183 and 209, α, β- DBE-DBCH, BTBPE, DBDPE, EH-TBB, BEH-TEBP and labelled internal standards (IS) 13C-BDE 209, 13C-BTBPE, 13C-BEH-TEBP and 13C-HBCDD were purchased from Wellington Laboratories (Guelph, ON, Canada). BDEs 77 and 128 (IS) were obtained from Accustandard (New Haven, CT, USA). TBBPA-BDBPE was purchased from Dr. Ehrenstorfer (Essex, UK). HBCDDs were obtained from Sigma-Aldrich Company Ltd. (Dorset, UK).

Target FRs

The FRs investigated in this study comprise: 8 PBDEs (BDEs # 28, 47, 99, 100, 153, 154, 183 and 209), 3 HBCDDs (α-, β- and γ-HBCDD) and 16 EFRs (α-DBE-DBCH, β-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP, DBDPE, tetrabromobisphenolA-bis(2,3-dibromopropyl) ether (TBBPA-BDBPE), pentabromotoluene (PBT), hexabromobenzene (HBB), pentabromobenzene (PBBz), tetrabromo-o-chlorotoluene (TBCT), 1,2,4,5-tetrabromo-3,6-dimethylbenzene (TBX), pentabromoethylbenzene (PBEB), 2,3-dibromopropyl 2,4,6-tribromophenyl ether (TBP-DBPE), syn- dechlorane plus (DDC-CO) and anti- DDC-CO).

Sample collection

Food samples. Samples of 14 different food groups were collected from two supermarkets representing national chains and one local market in Birmingham, UK during May and June 2015. Three samples of each food group were collected per retail outlet. Following purchase, equal weights of each of the three samples comprising each food group taken from each outlet were homogenised to provide a composite sample. It was not possible to collect all food groups

126 from each of the three outlets, so the number of composite samples analyzed varied between one
127 and three for each food group (Table 1). Following homogenization, all composite samples were
128 freeze dried and stored at -20 °C prior to analysis.

129 *Human milk samples.* Donors of all human milk samples were primiparas. Archived human milk
130 samples (n=25, each comprising ~50 mL) for which LFR data have been reported previously
131 (Abdallah and Harrad, 2014, 2011) were obtained from the milk bank of Birmingham Women's
132 Hospital after the research proposal and experimental design were approved by a local research
133 ethics committee (REC reference number: 9/H1211/57) according to UK National Health
134 Service guidelines (Abdallah and Harrad, 2014). Detailed sampling collection procedures are
135 provided elsewhere (Abdallah and Harrad, 2014), but in summary, following their collection
136 from primiparous mothers within their first three months of lactation in 2010, these archived
137 milk samples were transferred on ice from the milk bank in 100 mL clean polypropylene
138 containers and freeze dried prior to storage at -20 ºC until analysis.

139 Contemporary human milk samples (n=10, each comprising ~50 mL) were collected within the
140 first three months of birth from participants living in Southampton, UK, between August 2014
141 and May 2015 as part of the Breast milk, Environment, Early-life, and Development (BEED)
142 study conducted by researchers at Imperial College London (REC reference number:
143 13/NW/0202). After collection, samples were kept frozen in clean screw-capped polypropylene
144 containers and then transferred on ice from Imperial College London to Birmingham before
145 freeze drying and storage at -20 °C until the time of analysis.

146 **Estimation of daily dietary intakes**

147 Dietary intakes of the studied FRs were calculated for UK toddlers and adults based on food

consumption data from the latest national diet and nutrition survey report published by Public Health England and the Food Standards Agency (2014) (Table S8). Dietary intakes were calculated by multiplying food consumption rates for both average ("typical") and high-end consumers (the latter assumed to be those consuming the average consumption rate + 2 standard deviations) by average concentrations in each food group. More details are provided in the SI section.

Daily dietary intakes (DI) were calculated using Eq. (S1):

$$DI = \sum_{i=1}^{n} \frac{Ci * CRi}{B_W} \quad DI = \sum_{i=1}^{n} \frac{Ci * CRi}{B_W} \quad DI = \sum_{i=1}^{n} \frac{Ci * CRi}{B_W} \quad \text{..... Eq. (S1)}$$

Where ***Ci*** is the concentration (ng/g ww) of FR in a food item ***i*** and ***CRi*** is the daily consumption rate of the foodstuff ***i*** (g/day; values given in supporting material). Body weight (B_W; kg) values employed in this study were assumed to be 70 kg for and 10 kg for adults and toddlers, separately.

Estimation of infants' intake of FRs via breast milk

Breast milk is a recognized medium for direct transfer of POPs to nursing infants. We estimated a nursing infants' dietary intake of the studied FRs via breast milk using Eq. (S2):

$$DI = \frac{C_{FRs} * F_{lipid}}{B_W} \quad \text{..... Eq. (S2)}$$

Where ***DI*** is the estimated dietary intake (ng/kg bw/day); C_{FRs} is the concentration of target FRs in milk (ng/g lw); F_{lipid} is the daily lipid intake via breast milk (g/day) and B_W is the body weight. The infant's daily lipid intake via breast milk (F_{lipid}) was calculated using U.S. EPA guidelines (USEPA, 2002) which suggest an average intake of 702 mL milk per day for a 1 month old infant weighing 4.14 kg. The median lipid content of the analysed milk samples was 3.47 g lipid per 100 mL of breast milk resulting in a daily lipid intake of 24.4 g lipid/day.

First order pharmacokinetic (PK) model

To examine the relationship between our estimated intakes via various pathways and the body burdens indicated via levels in human milk, a simple one-compartment, first order pharmacokinetic (PK) model was used (Abdallah and Harrad, 2011). The studied FRs were hypothesized to accumulate in lipids (the single compartment in the model). Therefore, the change in FRs lipid level over time can be calculated by Eq. (S2):

$$\frac{\delta C_{FR}}{\delta t} = \frac{I_{FR}(t) * AF_{FR}}{BL(t)} - K_{FR} * C_{FR}(t) \quad \text{..... Eq. (S3)}$$

Where C_{FR} is the compound specific concentration in lipids (ng/g lw); I_{FR} is the daily intake of the target FR (ng/day); AF_{FR} is the absorption fraction; BL is body lipid mass (g) and K_{FR} is the compound specific first order dissipation rate (day^{-1}).

If K_{FR} is assumed constant over time, then Eq. (S3) can be changed into:

$$C_{FR}(t) = C_{FR}(0) * e^{(-K_{FR} * t)} + \left[\frac{I_{FR}(t) * AF_{FR}}{BL(t)}\right] * \left[\frac{(1 - e^{(-K_{FR} * t)})}{K_{FR}}\right] \quad \text{.....Eq. (S4)}$$

Where $C_{FR}(0)$ is the studied FR body lipid concentration at time 0 (initial concentration before intake). Assuming a constant dose over time at constant body lipid mass, the steady state BFR lipid concentration can be calculated from Eq. (S4):

$$C_{FR} = \frac{I_{FR}(t) * AF_{FR}}{BL(t) * K_{FR}} \quad \text{.....Eq. (S5)}$$

While Eq. (S5) is used to predict the body burdens of the target FRs, it is stressed that the assumption of steady state conditions is an inherent uncertainty with this approach.

To convert daily adult intakes of FRs via different exposure pathways to expected body burdens, the dust and diet absorption fractions and human half-lives for PBDEs and HBCDDs (Abdallah et al., 2012; Abdallah and Harrad, 2011; Geyer et al., 2004; Lorber, 2008; Thuresson et al., 2006) were used in Eq. (S4) (Table S16) while the inhalable fraction was assumed to be 100%

bioavailable. The body lipid mass was estimated based on a 25% body fat for an average adult weighing 70 kg (U.S. EPA, 1997). Finally, K_{FR} was calculated as $0.693/t_{0.5}$; where $t_{0.5}$ is the half-life of the studied FRs in the body lipid compartment (Table S16).

Analytical protocols

All samples were spiked with internal standards (^{13}C-BDE 209, ^{13}C-BTBPE, ^{13}C-BEH-TEBP, BDE 77, BDE 128) before extraction. Aliquots of freeze-dried human milk or diet samples (~500 mg) were accurately weighed and extracted using pressurized liquid extraction (Dionex ASE 350) with hexane/acetone (3:1, v/v). Extraction cells were filled from bottom to top with: pre-cleaned hydromatrix, 2 g Florisil®, 3 g alumina, samples, and then topped with hydromatrix. The crude extracts were further purified via shaking with 5-6 mL concentrated sulfuric acid before reconstitution in 50 µL iso-octane containing 250 pg/uL PCB-129 as recovery determination standard for QA/QC purposes.

Our analytical methods for measurement of target FRs have been described previously (Tao et al., 2016). In summary, analysis was conducted on a Trace 1310 GC coupled to an ISQ™ single quadrupole mass spectrometer (Thermo Scientific, TX, USA) operated in ECNI mode. After GC/MS analysis, the samples were evaporated and reconstituted in 200 µL of methanol containing d_{18}-γ-HBCD (25 pg/µL) as recovery determination standard for determination of HBCDDs by LC-MS/MS using a previously reported method (Harrad et al., 2009). Detailed description of the analytical methods and QA/QC measurements is provided in the supporting information (SI).

Quality Assurance/Quality Control

Five-point calibration curves were constructed for each target compound with excellent linearity

(R^2 > 0.99) over a concentration range relevant to those detected in air and dust samples. Average recoveries of IS were: 83 ± 16% for BDE-77, 95 ± 10% for BDE-128, 88 ± 11% for ^{13}C-BEH-TEBP, 89 ± 37% for ^{13}C-BTBPE, and 78 ± 25% for ^{13}C-BDE-209. Instrumental limits of detection (LOD) and method limits of quantification (LOQ) were calculated for each target compound based on 3:1 and 10:1 signal to noise ratio, respectively (Table S1). Granular anhydrous sodium sulfate (1 g) was extracted as a method blank. One method blank was prepared using the same analytical method for each batch of five samples. BDE-209 was detected in the majority of blanks but at a level below 5% of the levels detected in samples from the corresponding batch. None of the other target compounds were detected in method blanks for food and human milk samples.

Statistical Analysis

Statistical analysis of data was performed using both Excel (Microsoft Office 2010) and IBM SPSS Statistics 21.0 (Chicago, IL, U.S.A.). Data were checked for normality via the Kolmogorov-Smirnov test and visual inspection of quantile-by-quantile graphic plots in SPSS. When datasets were found to be log-normally distributed, further statistical analysis was performed on log-transformed data. Independent t-tests and ANOVA analyses were only conducted for target compounds with detection frequencies ≥60%. In instances where analyte levels were <LOQ, concentrations were assumed to equal LOQ/2.

Results and discussion

Concentrations of FRs in food

EFRs

Of all 16 target EFRs, only α-DBE-DBCH, β-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP,

DBDPE were found above the detection limit (Table S1) in the studied food samples. Table 1 summarizes the concentrations of EFRs in composite food samples collected in the UK. β-DBE-DBCH was detected in all samples, followed by α-DBE-DBCH and EH-TBB (detected in 97% and 77% of samples, respectively), while DBDPE was the least detected EFR with a detection frequency (DF) of 33%. β-DBE-DBCH was the predominant compound in the studied food samples, accounting for 64.5%±29.5% of ΣEFRs.

To the best of our knowledge, only one previous study has reported concentrations of DBE-DBCH in food samples as part of a Swedish market basket study (Sahlström et al., 2015). In this, DBE-DBCH was only found in four fish samples at levels (average 114 pg/g ww) lower than those in our study (fish: 240-1820 pg/g ww). Moreover, in the Swedish study, α-DBE-DBCH was the dominant EFR (Sahlström et al., 2015) in contrast to our data.

Very little is known about the levels of EFRs in UK food samples. A previous study of EFRs in a selection of UK and Irish food samples collected between June and August 2007 detected only BTBPE above the method LOQ and at levels (0.05-3.33 ng/g lw) comparable to those detected in our study (0.04 – 2.4 ng/g lw, Table S4) (Fernandes et al., 2010). With respect to fish, BTBPE and DBDPE were also detected in samples collected in Canada (Law et al., 2006), France (Munschy et al., 2011), and China (He et al., 2012; Li et al., 2015; Shi et al., 2009) at levels comparable to those found in our study (Table S4). Moreover, Labunska et al.(2015) detected BTBPE, EH-TBB, and BEH-TEBP in meat, fish, liver and egg samples from an e-waste processing area and control sites in South China, while Zheng et al. (2012) reported levels of BTBPE and DBDPE in chicken eggs from another South China e-waste processing area. In both studies, levels of EFRs in food items from e-waste recycling areas exceeded those detected in our

study, underlining the significance of informal e-waste recycling as a source of EFRs to the environment and the human diet (Table S4).

The isomeric ratio of β- to α-DBE-DBCH ($f_{\beta\text{-}DBE\text{-}DBCH} = \frac{Concentration\ of\ \beta-DBE-DBECH}{Concentration\ of\ \alpha-DBE-DBECH}$) in our food samples ranged from 1.2 to 220, with a median value of 7.3. In agreement with this finding, β-DBE-DBCH was reported as the predominant DBE-DBCH isomer in the blubber of Canadian arctic beluga (Tomy et al., 2008) and herring gull egg pools (Gauthier et al., 2008). Interestingly, the $f_{\beta\text{-DBE-DBCH}}$ values in our food samples significantly exceeded those detected in UK indoor dust (0.32-2.88) ($p<0.01$), indoor air (0.53-1.0) ($p<0.01$) (Tao et al., 2016) and the commercial product (1.0) (Arsenault et al., 2008), suggesting diastereomer-specific environmental degradation/metabolism, isomer-specific preferential uptake and/or isomerisation along the food chain. Furthermore, the median values of $f_{\beta\text{-DBE-DBCH}}$ in the analysed liver (80) and tuna (83) samples were substantially higher than those found in meat (5.9), eggs (7.1), cheese (2.1) and other fish (6.1). Moreover, the levels of DBE-DBCH were higher in liver than in other food samples studied except tuna (Table 1). These findings indicate that the uptake and metabolism of DBE-DBCH isomers might be species- and organism-dependent. This may be important given the reported toxicological effects of DBE-DBCH including reproductive toxicity and inducing aggressive behaviour in birds (Khalafet al., 2009; Marteinson et al., 2014).

LFRs

Tables 1, S5 and S6 show the average concentrations of LFRs detected in the studied composite food samples. Target PBDE congeners were frequently detected (DF > 70%). BDE 47 and BDE 99 were the major contributors to ΣPBDEs, consistent with previous studies of food samples from Spain (Domingo et al., 2008), the UK (Harrad et al., 2004) and the USA (Schecter et al.,

2009). The highest average concentrations were found in fish for ΣHBCDD (3.6-16 ng/g lw) and ΣPBDEs (14 to 40 ng/g lw). These levels were comparable to those found in the literature, with fish displaying higher concentrations of both ΣHBCDDs (Eljarrat et al., 2014; Goscinny et al., 2011; Schecter et al., 2009; Shi et al., 2009; Törnkvist et al., 2011) and ΣPBDEs (Bakker et al., 2008; Domingo et al., 2008; Törnkvist et al., UK Food and Environment Research Agency, 2009; 2011; UK Food Standards Agency, 2006; Voorspoels et al., 2007) than other food groups (Table S6). Moreover, concentrations of ΣHBCDD (<0.48-20 ng/g lw; <22-830 pg/g ww) in food samples in the current study were comparable to those detected in similar foodstuffs in two previous UK studies (<LOD-300 pg/g ww (Driffield et al., 2008) and 65-680 pg/g ww (UK Food Standards Agency, 2006), respectively) as well as those in other countries including: Romania (40-250 pg/g ww) (Dirtu and Covaci, 2010), Sweden (5.0-630 pg/g ww) (Törnkvist et al., 2011), Belgium (<10-350 pg/g ww) (Roosens et al., 2009), and the USA (nd-593 pg/g ww)(Schecter et al., 2009) but higher than those in China (<LOD-9.2 ng/g lw) (Shi et al., 2009). Average concentrations of ΣPBDEs in all UK food groups in the present study exceeded those reported elsewhere (Figure 1). The only exception was that the concentrations of ΣPBDEs in our fish samples were comparable to those reported in the Netherlands (Bakker et al., 2008). Concentrations of ∑PBDEs in the present study exceed those recorded in previous UK studies conducted in 2003-2004 and 2006 (Figure S1) (UK Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009). Recently, Rose et al. (2015) reported substantially high levels of ΣPBDEs in UK fresh water fish (average = 20 ng/g ww; maximum = 130 ng/g ww). However, we showed evidence of a temporal decline in concentrations of BDE 209 in office dust and of BDE 47 and 99 in office air in our recent UK study (Tao et al., 2016). This apparent contradiction may be attributable to a gradual shift over time of PBDEs from the indoor to the

303 outdoor environment of which one manifestation may be increasing concentrations of PBDEs in
304 the human diet (Harrad and Diamond, 2006). Furthermore, as BDE 209 has been reported to
305 debrominate to lower brominated PBDEs in both terrestrial and aquatic biota (Gandhi et al., 2011;
306 La Guardia et al., 2007; Letcher et al., 2014; Stapleton et al., 2006; Tian et al., 2012; Van den
307 Steen et al., 2007), it is plausible that ongoing transfer from the indoor environment to outdoors
308 and subsequent debromination of BDE 209 in biota, could drive temporal increases in
309 concentrations of lower congener PBDEs in food samples. This hypothesis is supported by the
310 relatively high ratios of tri-hexa-BDEs/BDE 209 in foodstuffs in this study compared to those in
311 two previous UK studies (Figure S2) even though levels of BDE-209 were comparable (UK
312 Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009) (Figure S3).

313 **Concentrations of FRs in human milk**

314 *EFRs*

315 Similar to food samples, α-DBE-DBCH, β-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP,
316 DBDPE were the only EFRs found in human milk samples. Table 2 shows a statistical summary
317 of concentrations of our target EFRs in archived human milk samples collected in 2010 (human
318 milk group 1) and human milk samples collected from 2014-2015 (human milk group 2). While
319 no statistically significant differences were found between concentrations of individual EFRs in
320 the two groups ($p>0.05$), the DFs of all EFRs in group 1 were lower than those in group 2. This
321 may indicate increased usage of these EFRs currently than hitherto. The DFs of DBDPE and
322 BTBPE were low (<50%) in both human milk groups, even though these two FRs were detected
323 in > 60% of UK indoor dust samples collected in 2014 (Tao et al., 2016). However, our results
324 are similar to DFs reported for these two FRs in 105 Canadian human milk samples collected in
325 2008-2009 (Zhou et al., 2014).

326 Current evidence about the capacity for bioaccumulation of DBDPE and BTBPE is equivocal.
327 Both flame retardants have been reported to display high bioaccumulation potential in fish (He et
328 al., 2012; Tomy et al., 2007). In contrast, findings for DBDPE and BTBPE in mammals such as
329 rats (Hakk et al., 2004; Nomeir et al., 1993; Verreault et al., 2007; Wang et al., 2010) and
330 chicken (Zheng et al., 2015) suggest low bioaccessibility and relatively high biotransformation
331 potential, consistent with the low DFs of these chemicals in our human milk samples.
332 Interestingly, very high levels of BTBPE (56 and 54 ng/g lw) were found in two archived (group
333 1) human milk samples, which may reflect elevated exposure to BTBPE of the individual donors
334 concerned - plausible given our recent detection in one UK dust sample of BTBPE at a
335 concentration of 4,700,000 ng/g (Tao et al., 2016).

336 In our study, EH-TBB was more frequently detected than BEH-TEBP in line with a previous
337 study of EFRs in human milk from Canada (Zhou et al., 2014). This may be associated with
338 higher bioaccessibility of EH-TBB compared to BEH-TEBP (Fang and Stapleton, 2014), and/or
339 by preferential partitioning of EH-TBB from blood to milk in humans relative to BEH-TEBP
340 (Zhou et al., 2014). Similar observations were made by Liu et al.(2016) i.e. EH-TBB was
341 detected more frequently than BEH-TEBP in human hair, fingernails, toenails and serum. This is
342 also in line with the reported greater lactational transfer of EH-TBB relative to BEH-TEBP in
343 dosed Wistar rats (Phillips et al., 2016).

344 Of our target EFRs, β-DBE-DBCH showed the highest DFs and concentrations in both human
345 milk groups (Table 1). To our knowledge, this is the first report of β-DBE-DBCH in human milk
346 samples worldwide. Sahlström et al. (2015) detected only α-DBE-DBCH in two pooled breast
347 milk samples in Sweden, at an average of 4.0 pg/g ww, well below the average concentrations
348 detected in our study (41 and 24 pg/g ww in human milk group 1 and group 2, respectively). In

line with our results in food items of animal origin, the values of $f_{\beta\text{-DBE-DBCH}}$ ranged from 0.9 to 608 across both human milk groups, with a median of 9.6. This exceeds significantly those in UK indoor air (0.53-1.0) and dust (0.32-2.88) ($p < 0.001$) indicating potential isomer-specific degradation/metabolism and/or bioisomerisation in humans. Of note, $f_{\beta\text{-DBE-DBCH}}$ values in human milk were statistically indistinguishable from those in diet samples ($p > 0.05$) indicating the relatively higher abundance of β-DBE-DBCH compared to α-DBE-DBCH in human milk may be at least partially attributable to dietary intake of DBE-DBCH.

Despite the ubiquity of EFRs in the environment, very few studies have reported on their levels in human tissues. In Canada, the reported concentrations of EH-TBB (nd-24 ng/g lw) in human milk samples (n=105) (Zhou et al., 2014) exceeded those in our study, while concentrations of BEH-TEBP (nd-6.6 ng/g lw) and DBDPE (nd-25 ng/g lw) were comparable to those reported here (Table 2). Of note, our concentrations of EH-TBB and BEH-TEBP in UK human milk were much lower than those detected in human hair, fingernails and toenails (EH-TBB: 7.6-4540 ng/g; BEH-TEBP: 13-2600 ng/g) as well as serum samples (TBB: 1.3-54 ng/g lw; BEH-TEBP: 19-69 ng/g) from the USA (Liu et al., 2016).

LFRs

Concentrations of Σtri-hexa-BDEs, BDE-209 and ΣHBCDDs in human milk group 1 and 2 are summarized in Table 2, with those for individual HBCDD diastereomers summarized in Table S6. Concentrations of ∑HBCDDs in human milk group 2 samples ranged between 0.7-7.1 ng/g lw, which were slightly - albeit not statistically significantly - lower than those in UK human milk group 1 (1.0-22.4 ng/g lw) (Abdallah and Harrad, 2011). While concentrations of ΣHBCDD in food samples in this study were comparable to those in two previous UK studies (Driffield et

al., 2008; UK Food Standards Agency, 2006), ΣHBCDDs in UK indoor air and dust collected between 2013 and 2015 appear lower than in samples collected between 2006 and 2007. This may account for the slight downward trend we observed for ΣHBCDDs in UK human milk.

The average concentration of Σtri-hexa-BDEs in group 2 (6.5 ng/g lw) is comparable to that reported for group 1 (5.9 ng/g lw) and to Australian human milk samples (7.6 ng/g lw) collected in 2007 (Toms et al., 2009). The relatively higher concentrations of BDE 153 compared to BDE 99 in this study concur with several previous studies (Abdallah and Harrad, 2014; Dunn et al., 2010; Frederiksen et al., 2009; Hassine et al., 2012). By comparison, in UK indoor air, dust (Tao et al., 2016) and diet samples (Table S5), concentrations of BDE 153 are exceeded substantially by those of BDE 99, indicating that external exposures through indoor air, dust and diet cannot account for the elevated abundance of BDE 153 in human milk. This higher relative abundance in humans of BDE-153 is more likely attributable to its higher bioaccumulation potential in lipids (as evidenced by a half-life of 6.5 years compared to 1.8 and 2.9 years for BDE-47 and BDE-99 respectively) and/or possible debromination of BDE 209 to BDE 153 (Abdallah and Harrad, 2014), consistent with the significant correlation between concentrations in human milk of BDE 153 and BDE 209 in this study ($p < 0.05$).

No significant differences were observed between concentrations of Σtri-hexa BDEs in human milk group 2 (collected in 2014-2015) and group 1 (collected in 2010) (Abdallah and Harrad, 2014) ($p > 0.05$) (Table S7). This is in agreement with previous studies reporting no significant change in concentrations of ΣPBDEs (*N.B.* BDE 209 not measured) in human milk samples collected between 2002 and 2007 in Spain (Schuhmacher et al., 2009) and between 2000 to 2009 in Taiwan (Shy et al., 2012). Similarly, concentrations of PBDEs in Canadian human milk

393 appear to have stabilised between 2002 and 2005 (Ryan and Rawn, 2014). As diet and dust have
394 been identified as the major pathways of human exposure to PBDEs (Harrad et al., 2008, 2004;
395 Lorber, 2008), it is intriguing that while concentrations of Σtri-hexa BDEs in our UK food
396 samples exceed those reported in two previous UK food surveys (Figure S4); no significant
397 temporal change was observed in concentrations of Σtri-hexa BDEs in UK dust over the studied
398 period (Tao et al., 2016) (2006-2007 to 2013-2015). These contrasting temporal trends in
399 concentrations of tri-hexa BDEs in UK diet and dust are not inconsistent with the hypothesis of
400 Harrad and Diamond (2006) that dietary exposure to chemicals with substantial indoor sources
401 (e.g. FRs) may continue to increase for some time after exposure via indoor pathways has
402 stabilised or fallen as a result of legislative curbs on use. Thus the steady concentrations of tri-
403 hexa-BDEs in human milk observed here may indicate the importance of dust relative to diet as a
404 vector of exposure of the UK population to these contaminants. Concentrations of BDE 209 in
405 human milk group 2 are indistinguishable from those in group 1 (Abdallah and Harrad, 2014) ($p > 0.05$)
406 (Table 2). This is consistent with the studies of Fängström et al. (2008) and Shy et al. (2012)
407 who also observed no time trend for BDE 209 in human milk samples in Sweden (between 1980-
408 2004) and Taiwan (between 2000-2009). Consistent with this, no substantial differences were
409 found between BDE 209 concentrations in food in the present study and those in two previous
410 UK dietary studies (Figure S3) (UK Food Standards Agency, 2006; UK Food and Environment
411 Research Agency, 2009). In contrast, concentrations of BDE 209 in UK office dust decreased
412 significantly over the period (2006-2007 to 2013-2015) (Harrad et al., 2008; Tao et al., 2016).
413 Notwithstanding the relatively small number of samples in the current study, this implies that
414 concentrations of this congener in dust exert a relatively minor influence on body burdens. This
415 may be attributable to the very low bioaccessibility from dust (7-14%) of BDE 209, combined

with its very short human half-life (7 days) and preferential partitioning to serum rather than milk fat (Abdallah and Harrad, 2014).

Relative abundance of various FRs

β-DBE-DBCH, BDE47 and BDE99 were the major target compounds in meat, fish, egg and dairy products, contributing 59%, 57% and 60% to ΣFRs in these food groups, respectively. In liver samples, β-DBE-DBCH was the predominant flame retardant, accounting for 69% of ∑FRs. As shown in Figure S5, PBDEs were the predominant FR class found in meat, fish, egg and dairy products, contributing 44%, 46% and 52% of ΣFRs, respectively. In contrast, EFRs were more prevalent in liver samples, accounting for 81% of ∑FRs.

BDE47 was the most abundant compound in human milk, contributing 20% of ΣFRs, followed by α-HBCDD and β-DBE-DBCH accounting for 17% and 11% of ΣFRs, respectively. PBDEs were the predominant FR class in human milk (Figure S6), contributing an average of 50% to ΣFRs, followed by EFRs (38% of ΣFRs). Despite the bans and restrictions on the use of PBDE commercial products, PBDEs remain the most abundant class out of our target FRs in human milk, which may reflect ongoing emissions of these LFRs from old furniture and appliances as well as long half-lives of some PBDE congeners (e.g. BDE 153) in human tissues.

Estimation of dietary intakes

EFRs

The estimated high-end and average dietary intakes of ∑EFRs in the UK were 26 and 89 ng/day (2.6 and 1.3 ng /body weight/day) for toddlers and adults, respectively (Table S9). The estimated high-end intakes were one order of magnitude higher than the average dietary intakes for both

toddlers and adults (Table S9). The main contributor to human dietary exposure to most EFRs and ∑EFRs was meat, followed by fish. However, consumption of eggs and dairy products was the principal contributor to dietary intakes of BEH-TEBP for both toddlers and adults (Figure S7). This is the first estimate of dietary exposure to EFRs for the UK. Furthermore, very limited information on human dietary exposure to EFRs has been reported anywhere to date. Estimated dietary intakes of EFRs for adults and children from an e-waste recycling area in eastern China were 756 and 1827 ng/day, respectively, which is much higher than those in our study (Labunska et al., 2015).

β-DBE-DBCH showed the highest contribution to the estimated ∑EFRs intakes in the present study for both adults and children (14 and 50 ng/day respectively). We are aware of a Swedish study on dietary exposure to EFRs in which EFRs were only detected in fish (Sahlström et al., 2015). The estimated median daily intakes of EFRs were 6.8 and 3.3 ng/day for Swedish mothers and toddlers, which is similar to our estimated daily intakes of EFRs through fish consumption (10 and 2.2 ng/day, respectively).

LFRs

Tables S10 and ~~S10~~S11 show the estimated intakes of ∑PBDEs via consumption of food in the UK and other different countries. An important caveat is that our estimates of dietary exposure are based on a limited range of food categories and a relatively small number of food items. Estimated average daily intakes of ∑PBDEs in our study are 42 and 124 ng/day for toddlers and adults, respectively, which is lower than one previous study by the UK Food Standards Agency (2006). This is comparable to estimates of dietary PBDEs intake in Spain (Domingo et al., 2008) but exceeds those for the USA (Schecter et al., 2009), Belgium (Voorspoels et al., 2007), the

Netherlands (Bakker et al., 2008), Sweden (Törnkvist et al., 2011), China (Su et al., 2012) and Romania (Dirtu and Covaci, 2010). Notably, estimated high-end intakes of ΣPBDEs were 5 times higher than the mean dietary intakes for both toddlers and adults (Table S10). Meat was the main source of PBDEs for both toddlers and adults in this study, contributing > 58% of the overall intake, consistent with previous studies conducted in China (Su et al., 2012) and Romania (Dirtu and Covaci, 2010). However, fish was the predominant contributor to human exposure of PBDEs in several other countries such as Sweden (Törnkvist et al., 2011), Belgium (Voorspoels et al., 2007), and Spain (Domingo et al., 2008).

Estimated average daily dietary intakes of ∑HBCDDs for UK adults and toddlers are 8.8 and 31 ng/day respectively (Table S12). Compared with other countries, our estimate of UK adult dietary intake of HBCDDs is comparable to those for the USA (Schecter et al., 2009), Sweden (Törnkvist et al., 2011) and China (Shi et al., 2009); but lower than those in one previous UK study (UK Food Standards Agency, 2006), Belgium (Goscinny et al., 2011), Spain (Eljarrat et al., 2014), the Netherlands (de Winter-Sorkina, 2003) and Romania (Dirtu and Covaci, 2010) (Table S13). Meat was the food group making the greatest contribution to dietary exposure to ΣHBCDDs (76% and 73% for toddlers and adults respectively), followed by fish (23% and 20% for toddlers and adults respectively). Elsewhere, meat was the main contributor to dietary exposure in the USA (Schecter et al., 2009), Belgium (Goscinny et al., 2011), Netherland (de Winter-Sorkina, 2003), China (Shi et al., 2009) and Romania (Dirtu and Covaci, 2010). In contrast, milk and fruit were the main contributors to dietary exposure to HBCDDs in a previous UK study (UK Food Standards Agency, 2006), while in Spain (Eljarrat et al., 2014) and Sweden (Törnkvist et al., 2011), fish was the main source of dietary intake of HBCDDs.

Nursing infants' dietary intake of FRs via breast milk

Table S14 and S15 summarise estimated intakes of target FRs via breast milk for a 1 month old infant (Further details are provided in the SI section). Estimated median dietary exposure to ΣEFRs of a breast-fed infant assuming ingestion of milk from group 2 was 18 ng/kg bw/day, thereby exceeding substantially our estimated average dietary intakes for both UK adults (1.1 ng/kg bw/day for 70 kg adults) and toddlers (2 ng/kg bw/day for 10 kg toddlers). Shi et al. (2016) reported an average ΣEFRs intake of 38.4 ng/kg bw/day for nursing infants in China, which is higher than our estimate. In Shi et al. (2016)'s study, the dietary intake of DBDPE was predominant, accounting for 87% to 99% of the total dietary intake of ΣEFRs, while in our study β-DBE-DBCH was the main contributor, with a contribution of 39% to the total dietary intake of ΣEFRs. The estimated dietary intakes of target EFRs from human milk group 1 were comparable to those from group 2. The dietary intakes of nursing infants of PBDEs and HBCDDs were previously reported using group 1 (collected in 2010) data (Abdallah and Harrad, 2014, 2011) and no substantial differences were observed between those and our estimates from group 2 data (collected in 2014-15).

Relationship between FR intake and human body burdens

To examine the relationship between estimated intakes via various pathways and human body burdens measured in human milk samples; a simple one-compartment, first order pharmacokinetic (PK) model was used (Abdallah and Harrad, 2011). Detailed information about the PK model and methods via which our predicted body burdens are derived are supplied in the SI section.

Despite limited information on the toxicokinetics of EH-TBB and BEH-TEBP in rodents

503 (Knudsen et al., 2016; 2017), to the best of our knowledge, no information is available for
504 bioavailable fractions and human half-lives of EFRs. We therefore estimated these parameters
505 for EFRs from those for related PBDEs (Table S16), e.g. those for DBE-DBCH (4 x Br;
506 molecular weight: 427.8) were assumed equivalent to that for BDE 47 (4 x Br; molecular weight:
507 485.79).

508 To our knowledge, this is the first attempt to model the body burden of EFRs in human milk. In
509 general, predicted adult body burdens agreed well with observed levels in human milk (Table 3).
510 Results revealed dietary exposure was the main contributor to UK adult body burdens of DBE-
511 DBCH and EH-TBB (64%-73%), while dust ingestion plays a more important role in driving
512 body burdens of BTBPE, BEH-TEBP, and DBDPE (61%-83% of body burden) in UK adults.
513 While human exposure to DBDPE via air and dust is relatively high, the low body burdens
514 observed for this EFR suggest low bioaccessibility and/or high biotransformation potential of
515 DBDPE as shown elsewhere for rats (Hakk et al., 2004; Nomeir et al., 1993;Verreault et al.,
516 2007; Wang et al., 2010) and chickens (Zheng et al., 2015). As our predicted body burdens were
517 based on assumed half-lives and absorption efficiencies of EFRs extrapolated from known values
518 for PBDEs, this good agreement indicates our target EFRs likely possess similar
519 physicochemical properties to PBDEs.

520 Overall, good agreement was observed between predicted and observed body burdens for our
521 target EFRs. This was achieved notwithstanding the simplicity of the PK model used, the
522 omission of dermal exposure, and for EFRs a number of additional factors such as: the scarcity
523 of information about crucial parameters like the half-lives of target compounds in human tissues,
524 and uncertainties about the bioaccessibility of target chemicals. While this suggests that we have
525 identified the principal exposure pathways to the target FRs, more research is needed to better

526 characterise exposure and factors that influence the relationship between external exposure and
527 body burdens for EFRs.

528 **Relationship between LFR intake and human body burdens**

529 Generally, predicted body burdens appear reasonably close to measured values of PBDEs in
530 human milk in the present study (Table S17). In a previous report, good agreement was also
531 observed between the predicted body burdens through diet, air and dust and the observed levels
532 of main target PBDEs in UK human milk (Abdallah and Harrad, 2014). In this study, dietary
533 intake was the major exposure pathway contributing to PBDE body burdens (56%-85% for tri-
534 hexa BDEs) in the UK population except for BDE 209 - for which dust ingestion accounted for
535 ~90% of overall body burden.

536 For HBCDDs, predicted body burdens were lower than observed levels for individual HBCDDs
537 in UK human milk when using our estimated dietary intake values of HBCDDs (Table S19).
538 This may be attributable to our focus on meat-related food samples in our study as HBCDD
539 concentrations were highest in vegetables, fruit and cows' milk in previous UK studies (Driffield
540 et al., 2008; UK Food Standards Agency, 2006). As concentrations of ∑HBCDDs in meat-
541 related food samples in this study were comparable to those reported previously (UK Food
542 Standards Agency, 2006), we therefore used estimated dietary intakes from this previous study to
543 predict body burdens. This resulted in closer agreement between predicted and observed body
544 burdens of individual HBCDDs. This indicates the importance of including vegetables, fruits,
545 milk and high water content food samples when monitoring dietary exposure to HBCDDs.

546 **Conclusions**

547 This study reveals the presence of EFRs in various types of UK food and human milk. Meat was

548 the main source of dietary intakes of PBDEs, EFRs and HBCDDs for both toddlers and adults
549 under an average consumer scenario. Estimated dietary exposures to EFRs were comparable to
550 dietary intakes of PBDEs but higher than those of HBCDDs for both toddlers and adults. The
551 most frequently detected compounds were α-DBE-DBCH, β-DBE-DBCH and EH-TBB in
552 human milk. This may be a health concern as some EFRs show similar persistence,
553 bioaccumulation potential and toxicity properties to legacy FRs (Bearr et al., 2010; Ezechiáš et
554 al., 2012; He et al., 2012; Howard and Muir, 2010; Johnson et al., 2013; Khalaf et al., 2009;
555 Pradhan et al., 2013; Saunders et al., 2013; Tomy et al., 2007), exacerbated by likely future
556 increases in use of EFRs due to the banned and restricted use of LFRs (European Court of Justice,
557 2008;La Guardia et al., 2006; Stockholm Convention, 2009; UNEP, 2014). In spite of recent
558 evidence of significant temporal trends for LFRs in food/indoor dust/air, no temporal changes
559 were observed for LFRs in human milk over the same time period. This suggests that the lag
560 time between changes in use of these chemicals and a response in human body burdens is not
561 insubstantial. We also examined the relationship between our estimated intakes via different
562 pathways and the body burdens using a simple one-compartment PK model. The results of this
563 showed predicted adult body burdens to be in agreement with observed levels in human milk for
564 all studied FRs. In summary, dust ingestion appears to constitute the major exposure pathway for
565 adults to BDE 209, BTBPE, BEH-TEBP, and DBDPE, while dietary exposure was the major
566 exposure pathway contributing to UK body burdens of HBCDDs, tri-hexa BDEs, DBE-DBCH
567 and EH-TBB.

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Supporting Information

Full details of the analytical protocols, QA/QC measurements and human exposure assessment models are provided as supporting information.

Tables

Table 1. Average concentrations of FRs in composite food samples from Birmingham, UK (ng/g lw)

	Lipid weight (%)	Water content (%)	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE	∑EFRs	BDE 209	∑tri-hexa BDEs	∑HBCDDs
Detection Frequency (%)	--	--	97%	100%	77%	60%	63%	33%	--	97%	--	--
Meat												
Beef (3[a])	8.0	67	0.89	1.9	0.20	<0.04	0.44	<1.1	4.5	0.46	15	2.7
Lamb (3)	8.0	68	0.62	6.2	0.19	<0.05	0.28	3.5	11	0.28	2.1	0.32
Pork (3)	8.0	66	0.95	4.1	1.4	2.4	0.20	4.6	14	0.42	21	4.6
Chicken (3)	5.0	73	0.58	7.6	0.36	1.3	0.57	<1.5	11	0.63	11	4.5
Liver												
Beef liver (2)	4.0	64	1.6	49	1.6	<0.06	0.69	4.5	57	3.3	32	20
Lamb liver (2)	5.0	65	<0.26	55	0.19	0.35	0.94	7.6	65	0.43	5.5	1.3
Pork liver (1)	5.0	69	1.1	85	0.63	0.24	5.0	1.5	93	0.51	4.7	7.9
Chicken liver (1)	4.0	73	0.72	34	0.66	0.14	5.8	<1.6	42	0.47	3.2	<0.48
Fish												
Salmon (3)	9.0	65	1.3	4.4	0.32	<0.04	<0.1	6.6	13	0.69	40	12
Mackerel (2)	20	49	1.1	4.9	0.22	0.17	<0.2	<0.63	7.0	0.74	13	3.6
Tuna (2)	2.0	75	0.48	39	0.38	0.78	0.42	21	62	1.7	16	16
Trout (2)	10	67	0.60	4.6	0.43	0.16	1.1	<0.88	7.4	0.34	27	8.8
Egg and dairy products												
Cheese (2)	18	46	0.44	0.99	0.11	0.20	0.22	<0.74	2.3	0.21	5.1	<0.24
Hen Eggs (1)	11	51	0.42	3.0	0.10	0.18	1.8	<1.2	6.1	0.53	1.9	1.3

[a]Number in parentheses denotes number of composite samples of that food group analysed.

588 **Table 2. Descriptive statistics for concentrations for EFRs and LFRs in UK human milk (ng/g lw) [a]**

	Lipid weight (%)	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE	∑EFRs	Σtri-hexa BDEs	BDE 209	∑HBCDDs
Human milk collected in 2010 (n=25)											
Detection Frequency	--	20%	76%	44%	28%	36%	4%	--	--	69%	--
Mean	3.2	--	6.8	--	--	--	--	--	5.9	0.31	5.95
Median	3.5	<0.13	3.1	<0.01	<0.1	<0.1	<0.78	7.9	5.00	0.25	3.83
Minimum	1.9	<0.13	<0.13	<0.01	<0.1	<0.1	<0.78	0.57	0.20	<0.06	1.04
Maximum	4.4	1.7	38	2.1	56	4.6	250	260	26.10	0.92	22.37
Human milk collected in 2014-2015 (n=10)											
Detection Frequency	--	100%	100%	90%	40%	50%	10%	--	--	40%	--
Mean	3.9	0.67	2.5	0.21	--	0.25	--	--	6.5	<0.22	3.2
Median	4.1	0.60	1.2	0.16	<0.1	<0.1	<0.78	3.1	5.8	<0.22	2.9
Minimum	1.5	0.30	0.43	<0.01	<0.1	<0.1	<0.78	1.9	1.7	<0.22	0.69
Maximum	5.3	1.1	10	0.48	0.71	0.73	58	59	14	0.67	7.1

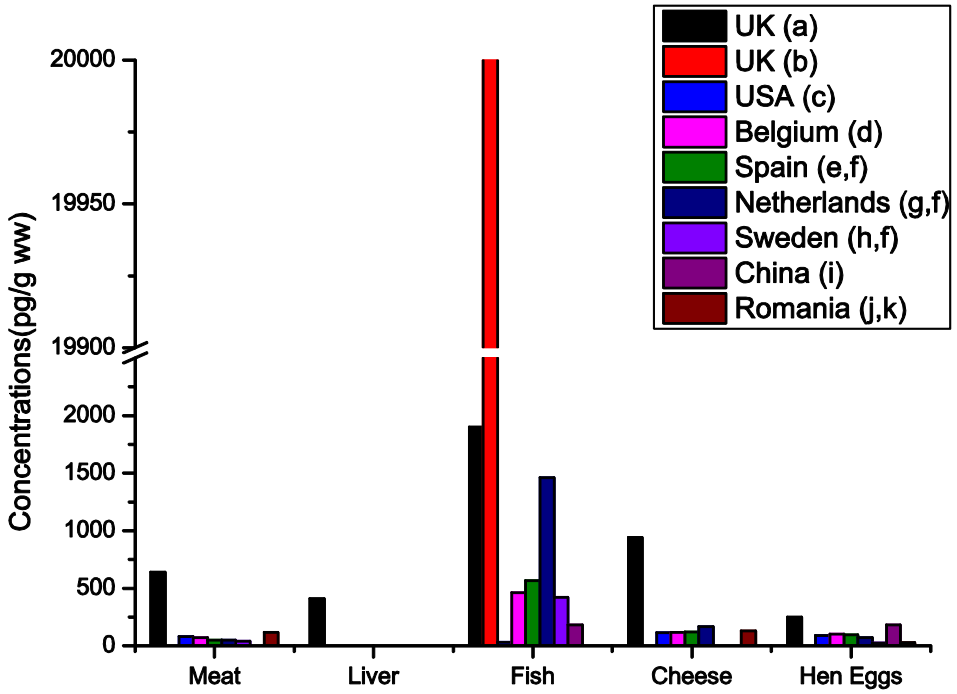
589 [a] Average concentrations were calculated only for those FRs for which detection frequency>50%.

Table 3. Estimated median and average daily intakes[a] of selected target EFRs and comparison of resultant predicted adult body burdens[b] with those observed in human milk

Exposure Pathway/EFR	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE
Average intake (ng/day)						
Dust[c]	0.26	0.30	0.97	21.00	14.00	20.00
Diet[d]	8.20	49.84	3.34	5.79	6.04	15.71
Air[c]	2.30	1.70	0.17	0.31	0.17	0.44
Median intake (ng/day)						
Dust[c]	0.16	0.18	0.19	1.50	2.60	6.50
Diet[d]	7.72	49.59	3.48	4.19	6.75	9.53
Air[c]	1.70	1.20	0.05	0.13	0.04	0.10
Average predicted body burdens (ng/g lw)						
Dust	0.01	0.02	0.04	0.15	0.10	0.003
Diet	0.43	2.61	0.15	0.04	0.04	0.003
Air	0.21	0.15	0.02	0.002	0.001	0.001
Sum	0.65	2.78	0.21	0.19	0.14	0.01
Median predicted body burdens (ng/g lw)						
Dust	0.01	0.01	0.01	0.01	0.02	0.001
Diet	0.40	2.60	0.16	0.03	0.05	0.002
Air	0.15	0.11	0.005	0.001	0.0003	0.0001
Sum	0.57	2.72	0.17	0.04	0.07	0.003
Observed body burdens (ng/g lw)						
Average	0.67	2.50	0.21	0.15	0.25	--
Median	0.60	1.20	0.16	<0.1	<0.1	<0.78

[a]Values below LOQ were assumed to be 1/2 LOQ. Average and median dust intakes based on assumption that 20 mg/day dust ingested (Jones-Otazo et al., 2005) containing the average and median FR concentrations reported for UK house dust and average inhalation rate of 20 m^3/day (Currado and Harrad, 1998);
[b]Body burdens were calculated only for those FRs for which detection frequency>50%;
[c]Data from Tao et al. (2016);
[d]Estimated from the average consumption rates calculated for each food group (Food Standards Agency, 2014), the average and median FRs concentrations in this study were used for calculation of average and median dietary intakes, separately.

599 **Figure 1. Average concentrations of ∑PBDEs (pg/g ww) in food samples from different countries.**



600

601 a) data from this study; b) date from Rose et al.(2015); c) data from Schecter et al.(2009); d) data from Voorspoels et al.(2007); e)

602 data from Domingo et al.(2008); f) BDE 209 was not measured; g) data from Bakker et al.(2008); h) data from Törnkvist et

603 al.(2011); i) data from Su et al.(2012); j) data from Dirtu and Covaci(2010); k) median concentrations of ∑PBDEs.

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Emerging and legacy flame retardants in UK human milk and food suggest slow response to restrictions on use of PBDEs and HBCDD

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Abstract

The legacy flame retardants (LFRs) polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD), together with six emerging flame retardants (EFRs) were measured in United Kingdom (UK) human milk collected in 2010 (n=25) and 2014-15 (n=10). These data are the first report of the presence of EFRs in UK human milk. The most abundant EFR was β-tetrabromoethylcyclohexane (DBE-DBCH) (average = 2.5 ng/g lw; geometric mean = 1.5 ng/g lw), which is comparable to the concentrations of the most abundant LFRs i.e. BDE 47 and α-HBCDD at 2.8 and 2.1 ng/g lw, respectively (geometric mean = 2.1 and 1.7). The estimated average dietary intake of ΣEFRs by UK nursing infants was 18 ng/kg bw/day. EFRs were also measured in UK foodstuffs with β-DBE-DBCH again the predominant compound detected, accounting – on average – for 64.5±23.4% of ΣEFRs. Average estimated dietary intakes of ∑EFRs in the UK were 89 and 26 ng/day (1.3 and 2.6 ng /body weight/day) for adults and toddlers, respectively. Concentrations of Σtri-hexa BDEs in our UK food samples exceeded those reported in UK samples from the same food categories collected in 2003-04 and 2006. Despite this and our recent report elsewhere of significant temporal declines in concentrations of BDE 209 in UK indoor dust ($p < 0.05$) and HBCDDs in UK indoor dust and air ($p < 0.001$), no significant temporal differences ($p > 0.05$) were observed between concentrations of Σtri-hexa BDEs, BDE 209 and HBCDDs in human milk sampled in 2010 and those obtained in 2014-15. UK adult body burdens for EFRs were predicted via inhalation, diet and dust ingestion using a simple pharmacokinetic model. The predicted EFR body burdens compared well with observed concentrations in human milk.

Keywords: Emerging flame retardants; Brominated flame retardants; Human exposure; Human milk; Diet; Nursing infant.

Highlights:

- First investigation of EFRs in UK human milk.
- Estimated dietary exposures to EFRs comparable to dietary intakes of PBDEs.
- β-DBE-DBCH most abundant EFR in food and human milk.
- No significant change in PBDEs and HBCDD in human milk between 2010 and 2014-15
- Nursing infant exposure to EFRs exceeds adult and toddler dietary intakes.
- Observed body burdens of EFRs match closely those predicted via PK modelling

Introduction

Flame retardants have been incorporated within a wide range of consumer goods and materials to meet fire safety regulations. Due to their persistent, bioaccumulative and toxic properties, legacy flame retardants (LFRs) like polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDDs) were subject to various bans and restrictions under different jurisdictions. Penta- and Octa-BDE technical products were banned in Europe (including the UK) by 2004, and globally under the UNEP Stockholm Convention in 2009. Significant restrictions have been put on the Deca-BDE technical product in Europe since 2008, while HBCDD was listed under the Stockholm Convention in 2014 (European Court of Justice, 2008; Stockholm Convention, 2009; UNEP, 2014). This resulted in increasing concerns over the use of emerging flame retardants (EFRs) to replace the banned LFRs. Previous studies have highlighted substantially higher levels of BDE-209 in UK indoor dust compared to other European countries, which was mainly attributed to the extensive usage of Deca-BDE in upholstery fabrics and textiles in the UK (1,000-1,200 tonnes/year out of an estimated 1,500 tonnes/year in the EU for this application) to comply with the stringent UK Furniture and Furnishing Fire Safety Regulation 1988 (EU risk assessment report, 2002). While concentrations of LFRs have been decreasing in UK indoor air and dust over the last decade, those of EFRs have been reported as increasing in the UK indoor environment (Tao et al., 2016). Moreover, the occurrence of EFRs has been widely documented recently in several environmental and biological matrices including indoor/outdoor air, indoor dust, soil, sediment, dietary items of animal origin, fish and birds (Cequier et al., 2014;Labunska et al., 2015; Li et al., 2015; Möller et al., 2011; Newton et al., 2015; Shi et al., 2009; Yang et al., 2012). This is of concern due to reports suggesting some EFRs (e.g. decabromodiphenyl ethane (DBDPE), 1,2-bis(2,4,6-

71 tribromophenoxy)ethane (BTBPE), EH-TBB and DBE-DBCH) are potentially persistent and
72 bioaccumulative (He et al., 2012; Howard and Muir, 2010; Patisaul et al., 2013; Tomy et al.,
73 2007). As a result, concentrations of EFRs in the human diet and tissues may increase in the
74 future.
75 Given their similar structure to LFRs, EFRs may pose similar adverse effects to those displayed
76 by LFRs. EFRs like DBE-DBCH, BTBPE, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB)
77 and bis(2-ethylhexyl)-tetrabromophthalate (BEH-TEBP) are capable of endocrine disruption and
78 DNA damage (Bearr et al., 2010; Ezechiáš et al., 2012; Johnson et al., 2013; Khalafet al., 2009;
79 Pradhan et al., 2013; Saunders et al., 2013). Despite such health concerns and evidence of
80 exposure via indoor air and dust, very limited information on levels of EFRs in the human diet
81 and human tissues exists to date. We are aware of only one UK and Irish diet study targeting
82 hexabromobenzene (HBB), DBDPE and BTBPE, in which only BTBPE was detected in some
83 UK food samples at concentrations ranging from 0.05-1.76 ng/g lw (Fernandes et al., 2010).
84 Elsewhere, in a Swedish market basket study, EFRs were only detected in fish samples collected
85 in 2010, with DBE-DBCH the predominant compound (Sahlström et al., 2015). In the same
86 study, α-DBE-DBCH was found in two Swedish pooled human milk samples (average = 4 pg/g
87 wet weight) collected in 2009-2010 (Sahlström et al., 2015). In the Sherbrooke region of Canada,
88 Zhou et al. (2014) measured several EFRs including EH-TBB, BEH-TEBP, BTBPE, and
89 DBDPE in paired human maternal serum (n = 102) and breast milk (n = 105) samples collected
90 in 2008-2009. EH-TBB was detected in > 55% of both serum and milk samples, while BEH-
91 TEBP, BTBPE, and DBDPE were also present but less frequently detected in both matrices
92 (Zhou et al., 2014).
93 In the present study, 16 EFRs were investigated in 14 groups of composite food samples

94 covering meat, liver, oily fish, eggs and cheese to provide a preliminary estimate of UK dietary
95 exposure. Additionally, concentrations of 8 PBDEs and 3 HBCDD diastereomers were measured
96 in the same samples and compared with those reported in previous UK studies to evaluate the
97 impact of regulations and restrictions on these LFRs. Moreover, this study measures the
98 concentrations of EFRs in UK human milk for the first time, compares exposures of nursing
99 infants with that of adults and toddlers, and uses a simple one-compartment pharmacokinetic
100 model to forecast the body burdens of the studied EFRs and LFRs in UK adults and compare
101 these predicted burdens to those derived empirically from the analysed human milk samples.

102 ## Materials and methods

103 ### Chemicals and reagents

104 Solvents used were all of HPLC analytical grade (Fisher Scientific, Loughborough, UK).
105 Standards of BDEs 28, 47, 99, 100, 153, 154, 183 and 209, α, β- DBE-DBCH, BTBPE, DBDPE,
106 EH-TBB, BEH-TEBP and labelled internal standards (IS) ^{13}C-BDE 209, ^{13}C-BTBPE, ^{13}C-BEH-
107 TEBP and ^{13}C-HBCDD were purchased from Wellington Laboratories (Guelph, ON, Canada).
108 BDEs 77 and 128 (IS) were obtained from Accustandard (New Haven, CT, USA). TBBPA-
109 BDBPE was purchased from Dr. Ehrenstorfer (Essex, UK). HBCDDs were obtained from
110 Sigma-Aldrich Company Ltd. (Dorset, UK).

111 ### Target FRs

112 The FRs investigated in this study comprise: 8 PBDEs (BDEs # 28, 47, 99, 100, 153, 154, 183
113 and 209), 3 HBCDDs (α-, β- and γ-HBCDD) and 16 EFRs (α-DBE-DBCH, β-DBE-DBCH, EH-
114 TBB, BTBPE, BEH-TEBP, DBDPE, tetrabromobisphenolA-bis(2,3-dibromopropyl) ether
115 (TBBPA-BDBPE), pentabromotoluene (PBT), hexabromobenzene (HBB), pentabromobenzene
116 (PBBz), tetrabromo-o-chlorotoluene (TBCT), 1,2,4,5-tetrabromo-3,6-dimethylbenzene (TBX),

117 pentabromoethylbenzene (PBEB), 2,3-dibromopropyl 2,4,6-tribromophenyl ether (TBP-DBPE),
118 syn- dechlorane plus (DDC-CO) and anti- DDC-CO).

119 **Sample collection**

120 *Food samples*. Samples of 14 different food groups were collected from two supermarkets
121 representing national chains and one local market in Birmingham, UK during May and June
122 2015. Three samples of each food group were collected per retail outlet. Following purchase,
123 equal weights of each of the three samples comprising each food group taken from each outlet
124 were homogenised to provide a composite sample. It was not possible to collect all food groups
125 from each of the three outlets, so the number of composite samples analysed varied between one
126 and three for each food group (Table 1). Following homogenisation, all composite samples were
127 freeze dried and stored at -20 °C prior to analysis.

128 *Human milk samples.* Donors of all human milk samples were primiparas. Archived human milk
129 samples (n=25, each comprising ~50 mL) for which LFR data have been reported previously
130 (Abdallah and Harrad, 2014, 2011) were obtained from the milk bank of Birmingham Women's
131 Hospital after the research proposal and experimental design were approved by a local research
132 ethics committee (REC reference number: 9/H1211/57) according to UK National Health
133 Service guidelines (Abdallah and Harrad, 2014). Detailed sampling collection procedures are
134 provided elsewhere (Abdallah and Harrad, 2014), but in summary, following their collection
135 from primiparous mothers within their first three months of lactation in 2010, these archived
136 milk samples were transferred on ice from the milk bank in 100 mL clean polypropylene
137 containers and freeze dried prior to storage at -20 ºC until analysis.
138 Contemporary human milk samples (n=10, each comprising ~50 mL) were collected within the
139 first three months of birth from participants living in Southampton, UK, between August 2014

and May 2015 as part of the Breast milk, Environment, Early-life, and Development (BEED) study conducted by researchers at Imperial College London (REC reference number: 13/NW/0202). After collection, samples were kept frozen in clean screw-capped polypropylene containers and then transferred on ice from Imperial College London to Birmingham before freeze drying and storage at -20 °C until the time of analysis.

Estimation of daily dietary intakes

Dietary intakes of the studied FRs were calculated for UK toddlers and adults based on food consumption data from the latest national diet and nutrition survey report published by Public Health England and the Food Standards Agency (2014) (Table S8). Dietary intakes were calculated by multiplying food consumption rates for both average ("typical") and high-end consumers (the latter assumed to be those consuming the average consumption rate + 2 standard deviations) by average concentrations in each food group. More details are provided in the SI section.

Daily dietary intakes (DI) were calculated using Eq. (S1):

$$DI = \sum_{i=1}^{n} \frac{Ci * CRi}{B_W} \quad \text{..... Eq. (S1)}$$

Where ***Ci*** is the concentration (ng/g ww) of FR in a food item ***i*** and ***CRi*** is the daily consumption rate of the foodstuff ***i*** (g/day; values given in supporting material). Body weight (B_W; kg) values employed in this study were assumed to be 70 kg for and 10 kg for adults and toddlers, separately.

Estimation of infants' intake of FRs via breast milk

Breast milk is a recognized medium for direct transfer of POPs to nursing infants. We estimated a nursing infants' dietary intake of the studied FRs via breast milk using Eq. (S2):

$$DIi = \frac{C_{FRs} * F_{lipid}}{B_W} \quad \text{..... Eq. (S2)}$$

Where ***DI*** is the estimated dietary intake (ng/kg bw/day); C_{FRs} is the concentration of target FRs in milk (ng/g lw); F_{lipid} is the daily lipid intake via breast milk (g/day) and B_W is the body weight. The infant's daily lipid intake via breast milk (F_{lipid}) was calculated using U.S. EPA guidelines (USEPA, 2002) which suggest an average intake of 702 mL milk per day for a 1 month old infant weighing 4.14 kg. The median lipid content of the analysed milk samples was 3.47 g lipid per 100 mL of breast milk resulting in a daily lipid intake of 24.4 g lipid/day.

First order pharmacokinetic (PK) model

To examine the relationship between our estimated intakes via various pathways and the body burdens indicated via levels in human milk, a simple one-compartment, first order pharmacokinetic (PK) model was used (Abdallah and Harrad, 2011). The studied FRs were hypothesized to accumulate in lipids (the single compartment in the model). Therefore, the change in FRs lipid level over time can be calculated by Eq. (S2):

$$\frac{\delta C_{FR}}{\delta t} = \frac{I_{FR}(t) * AF_{FR}}{BL(t)} - K_{FR} * C_{FR}(t) \quad \text{..... Eq. (S3)}$$

Where C_{FR} is the compound specific concentration in lipids (ng/g lw); I_{FR} is the daily intake of the target FR (ng/day); AF_{FR} is the absorption fraction; BL is body lipid mass (g) and K_{FR} is the compound specific first order dissipation rate (day^{-1}).

If K_{FR} is assumed constant over time, then Eq. (S3) can be changed into:

$$C_{FR}(t) = C_{FR}(0) * e^{(-K_{FR} * t)} + \left[\frac{I_{FR}(t) * AF_{FR}}{BL(t)}\right] * \left[\frac{(1 - e^{(-K_{FR} * t)})}{K_{FR}}\right] \quad \text{.....Eq. (S4)}$$

Where $C_{FR}(0)$ is the studied FR body lipid concentration at time 0 (initial concentration before intake). Assuming a constant dose over time at constant body lipid mass, the steady state BFR

183 lipid concentration can be calculated from Eq. (S4):

184 $$C_{FR} = \frac{I_{FR}(t) * AF_{FR}}{BL(t) * K_{FR}}$$ .....Eq. (S5)

185 While Eq. (S5) is used to predict the body burdens of the target FRs, it is stressed that the
186 assumption of steady state conditions is an inherent uncertainty with this approach.
187 To convert daily adult intakes of FRs via different exposure pathways to expected body burdens,
188 the dust and diet absorption fractions and human half-lives for PBDEs and HBCDDs (Abdallah
189 et al., 2012; Abdallah and Harrad, 2011; Geyer et al., 2004; Lorber, 2008; Thuresson et al., 2006)
190 were used in Eq. (S4) (Table S16) while the inhalable fraction was assumed to be 100 %
191 bioavailable. The body lipid mass was estimated based on a 25 % body fat for an average adult
192 weighing 70 kg (U.S. EPA, 1997). Finally, K_{FR} was calculated as $0.693/t_{0.5}$; where $t_{0.5}$ is the half-
193 life of the studied FRs in the body lipid compartment (Table S16).
194 **Analytical protocols**
195 All samples were spiked with internal standards (^{13}C-BDE 209, ^{13}C-BTBPE, ^{13}C-BEH-TEBP,
196 BDE 77, BDE 128) before extraction. Aliquots of freeze-dried human milk or diet samples (~500
197 mg) were accurately weighed and extracted using pressurised liquid extraction (Dionex ASE 350)
198 with hexane/acetone (3:1, v/v). Extraction cells were filled from bottom to top with: pre-cleaned
199 hydromatrix, 2 g Florisil®, 3 g alumina, samples, and then topped with hydromatrix. The crude
200 extracts were further purified via shaking with 5-6 mL concentrated sulfuric acid before
201 reconstitution in 50 µL iso-octane containing 250 pg/uL PCB-129 as recovery determination
202 standard for QA/QC purposes.

203 Our analytical methods for measurement of target FRs have been described previously (Tao et al.,
204 2016). In summary, analysis was conducted on a Trace 1310 GC coupled to an ISQ™ single

quadrupole mass spectrometer (Thermo Scientific, TX, USA) operated in ECNI mode. After GC/MS analysis, the samples were evaporated and reconstituted in 200 μL of methanol containing d_{18}-γ-HBCD (25 pg/μL) as recovery determination standard for determination of HBCDDs by LC-MS/MS using a previously reported method (Harrad et al., 2009). Detailed description of the analytical methods and QA/QC measurements is provided in the supporting information (SI).

Quality Assurance/Quality Control

Five-point calibration curves were constructed for each target compound with excellent linearity ($R^2 > 0.99$) over a concentration range relevant to those detected in air and dust samples. Average recoveries of IS were: 83 ± 16 % for BDE-77, 95 ± 10 % for BDE-128, 88 ± 11 % for ^{13}C-BEH-TEBP, 89 ± 37 % for ^{13}C-BTBPE, and 78 ± 25 % for ^{13}C-BDE-209. Instrumental limits of detection (LOD) and method limits of quantification (LOQ) were calculated for each target compound based on 3:1 and 10:1 signal to noise ratio, respectively (Table S1). Granular anhydrous sodium sulfate (1 g) was extracted as a method blank. One method blank was prepared using the same analytical method for each batch of five samples. BDE-209 was detected in the majority of blanks but at a level below 5 % of the levels detected in samples from the corresponding batch. None of the other target compounds were detected in method blanks for food and human milk samples.

Statistical Analysis

Statistical analysis of data was performed using both Excel (Microsoft Office 2010) and IBM SPSS Statistics 21.0 (Chicago, IL, U.S.A.). Data were checked for normality via the Kolmogorov-Smirnov test and visual inspection of quantile-by-quantile graphic plots in SPSS.

When datasets were found to be log-normally distributed, further statistical analysis was performed on log-transformed data. Independent t-tests and ANOVA analyses were only conducted for target compounds with detection frequencies ≥60 %. In instances where analyte levels were <LOQ, concentrations were assumed to equal LOQ/2.

Results and discussion

Concentrations of FRs in food

EFRs

Of all 16 target EFRs, only α-DBE-DBCH, β-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP, DBDPE were found above the detection limit (Table S1) in the studied food samples. Table 1 summarises the concentrations of EFRs in composite food samples collected in the UK. β-DBE-DBCH was detected in all samples, followed by α-DBE-DBCH and EH-TBB (detected in 97 % and 77 % of samples, respectively), while DBDPE was the least detected EFR with a detection frequency (DF) of 33 %. β-DBE-DBCH was the predominant compound in the studied food samples, accounting for 64.5 %±29.5 % of ΣEFRs.

To the best of our knowledge, only one previous study has reported concentrations of DBE-DBCH in food samples as part of a Swedish market basket study (Sahlström et al., 2015). In this, DBE-DBCH was only found in four fish samples at levels (average 114 pg/g ww) lower than those in our study (fish: 240-1820 pg/g ww). Moreover, in the Swedish study, α-DBE-DBCH was the dominant EFR (Sahlström et al., 2015) in contrast to our data.

Very little is known about the levels of EFRs in UK food samples. A previous study of EFRs in a selection of UK and Irish food samples collected between June and August 2007 detected only

BTBPE above the method LOQ and at levels (0.05-3.33 ng/g lw) comparable to those detected in our study (0.04 – 2.4 ng/g lw, Table S4) (Fernandes et al., 2010). With respect to fish, BTBPE and DBDPE were also detected in samples collected in Canada (Law et al., 2006), France (Munschy et al., 2011), and China (He et al., 2012; Li et al., 2015; Shi et al., 2009) at levels comparable to those found in our study (Table S4). Moreover, Labunska et al. (2015) detected BTBPE, EH-TBB, and BEH-TEBP in meat, fish, liver and egg samples from an e-waste processing area and control sites in South China, while Zheng et al. (2012) reported levels of BTBPE and DBDPE in chicken eggs from another South China e-waste processing area. In both studies, levels of EFRs in food items from e-waste recycling areas exceeded those detected in our study, underlining the significance of informal e-waste recycling as a source of EFRs to the environment and the human diet (Table S4).

The isomeric ratio of β- to α-DBE-DBCH ($f_{\beta\text{-}DBE\text{-}DBCH} = \frac{Concentration\ of\ \beta - DBE - DBECH}{Concentration\ of\ \alpha - DBE - DBECH}$) in our food samples ranged from 1.2 to 220, with a median value of 7.3. In agreement with this finding, β-DBE-DBCH was reported as the predominant DBE-DBCH isomer in the blubber of Canadian arctic beluga (Tomy et al., 2008) and herring gull egg pools (Gauthier et al., 2008). Interestingly, the $f_{\beta\text{-}DBE\text{-}DBCH}$ values in our food samples significantly exceeded those detected in UK indoor dust (0.32-2.88) ($p<0.01$), indoor air (0.53-1.0) ($p<0.01$) (Tao et al., 2016) and the commercial product (1.0) (Arsenault et al., 2008), suggesting diastereomer-specific environmental degradation/metabolism, isomer-specific preferential uptake and/or isomerisation along the food chain. Furthermore, the median values of $f_{\beta\text{-}DBE\text{-}DBCH}$ in the analysed liver (80) and tuna (83) samples were substantially higher than those found in meat (5.9), eggs (7.1), cheese (2.1) and other fish (6.1). Moreover, the levels of DBE-DBCH were higher in liver than in other

food samples studied except tuna (Table 1). These findings indicate that the uptake and metabolism of DBE-DBCH isomers might be species- and organism-dependent. This may be important given the reported toxicological effects of DBE-DBCH including reproductive toxicity and inducing aggressive behaviour in birds (Khalafet al., 2009; Marteinson et al., 2014).

LFRs

Tables 1, S5 and S6 show the average concentrations of LFRs detected in the studied composite food samples. Target PBDE congeners were frequently detected (DF > 70%). BDE 47 and BDE 99 were the major contributors to ΣPBDEs, consistent with previous studies of food samples from Spain (Domingo et al., 2008), the UK (Harrad et al., 2004) and the USA (Schecter et al., 2009). The highest average concentrations were found in fish for ΣHBCDD (3.6-16 ng/g lw) and ΣPBDEs (14 to 40 ng/g lw). These levels were comparable to those found in the literature, with fish displaying higher concentrations of both ΣHBCDDs (Eljarrat et al., 2014; Goscinny et al., 2011; Schecter et al., 2009; Shi et al., 2009; Törnkvist et al., 2011) and ΣPBDEs (Bakker et al., 2008; Domingo et al., 2008; Törnkvist et al., UK Food and Environment Research Agency, 2009; 2011; UK Food Standards Agency, 2006; Voorspoels et al., 2007) than other food groups (Table S6). Moreover, concentrations of ΣHBCDD (<0.48-20 ng/g lw; <22-830 pg/g ww) in food samples in the current study were comparable to those detected in similar foodstuffs in two previous UK studies (<LOD-300 pg/g ww (Driffield et al., 2008) and 65-680 pg/g ww (UK Food Standards Agency, 2006), respectively) as well as those in other countries including: Romania (40-250 pg/g ww) (Dirtu and Covaci, 2010), Sweden (5.0-630 pg/g ww) (Törnkvist et al., 2011), Belgium (<10-350 pg/g ww) (Roosens et al., 2009), and the USA (nd-593 pg/g ww) (Schecter et al., 2009) but higher than those in China (<LOD-9.2 ng/g lw) (Shi et al., 2009). Average concentrations of ΣPBDEs in all UK food groups in the present study exceeded those

293 reported elsewhere (Figure 1). The only exception was that the concentrations of ΣPBDEs in our
294 fish samples were comparable to those reported in the Netherlands (Bakker et al., 2008).
295 Concentrations of ∑PBDEs in the present study exceed those recorded in previous UK studies
296 conducted in 2003-2004 and 2006 (Figure S1) (UK Food Standards Agency, 2006; UK Food and
297 Environment Research Agency, 2009). Recently, Rose et al. (2015) reported substantially high
298 levels of ΣPBDEs in UK fresh water fish (average = 20 ng/g ww; maximum = 130 ng/g ww).
299 However, we showed evidence of a temporal decline in concentrations of BDE 209 in office dust
300 and of BDE 47 and 99 in office air in our recent UK study (Tao et al., 2016). This apparent
301 contradiction may be attributable to a gradual shift over time of PBDEs from the indoor to the
302 outdoor environment of which one manifestation may be increasing concentrations of PBDEs in
303 the human diet (Harrad and Diamond, 2006). Furthermore, as BDE 209 has been reported to
304 debrominate to lower brominated PBDEs in both terrestrial and aquatic biota (Gandhi et al., 2011;
305 La Guardia et al., 2007; Letcher et al., 2014; Stapleton et al., 2006; Tian et al., 2012; Van den
306 Steen et al., 2007), it is plausible that ongoing transfer from the indoor environment to outdoors
307 and subsequent debromination of BDE 209 in biota, could drive temporal increases in
308 concentrations of lower congener PBDEs in food samples. This hypothesis is supported by the
309 relatively high ratios of tri-hexa-BDEs/BDE 209 in foodstuffs in this study compared to those in
310 two previous UK studies (Figure S2) even though levels of BDE-209 were comparable (UK
311 Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009) (Figure S3).

312 **Concentrations of FRs in human milk**

313 *EFRs*

314 Similar to food samples, α-DBE-DBCH, β-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP,
315 DBDPE were the only EFRs found in human milk samples. Table 2 shows a statistical summary

316 of concentrations of our target EFRs in archived human milk samples collected in 2010 (human
317 milk group 1) and human milk samples collected from 2014-2015 (human milk group 2). While
318 no statistically significant differences were found between concentrations of individual EFRs in
319 the two groups ($p>0.05$), the DFs of all EFRs in group 1 were lower than those in group 2. This
320 may indicate increased usage of these EFRs currently than hitherto. The DFs of DBDPE and
321 BTBPE were low (<50 %) in both human milk groups, even though these two FRs were detected
322 in >60 % of UK indoor dust samples collected in 2014 (Tao et al., 2016). However, our results
323 are similar to DFs reported for these two FRs in 105 Canadian human milk samples collected in
324 2008-2009 (Zhou et al., 2014).

325 Current evidence about the capacity for bioaccumulation of DBDPE and BTBPE is equivocal.
326 Both flame retardants have been reported to display high bioaccumulation potential in fish (He et
327 al., 2012; Tomy et al., 2007). In contrast, findings for DBDPE and BTBPE in mammals such as
328 rats (Hakk et al., 2004; Nomeir et al., 1993; Verreault et al., 2007; Wang et al., 2010) and
329 chicken (Zheng et al., 2015) suggest low bioaccessibility and relatively high biotransformation
330 potential, consistent with the low DFs of these chemicals in our human milk samples.
331 Interestingly, very high levels of BTBPE (56 and 54 ng/g lw) were found in two archived (group
332 1) human milk samples, which may reflect elevated exposure to BTBPE of the individual donors
333 concerned - plausible given our recent detection in one UK dust sample of BTBPE at a
334 concentration of 4,700,000 ng/g (Tao et al., 2016).

335 In our study, EH-TBB was more frequently detected than BEH-TEBP in line with a previous
336 study of EFRs in human milk from Canada (Zhou et al., 2014). This may be associated with
337 higher bioaccessibility of EH-TBB compared to BEH-TEBP (Fang and Stapleton, 2014), and/or
338 by preferential partitioning of EH-TBB from blood to milk in humans relative to BEH-TEBP

339 (Zhou et al., 2014). Similar observations were made by Liu et al.(2016) i.e. EH-TBB was
340 detected more frequently than BEH-TEBP in human hair, fingernails, toenails and serum. This is
341 also in line with the reported greater lactational transfer of EH-TBB relative to BEH-TEBP in
342 dosed Wistar rats (Phillips et al., 2016).

343 Of our target EFRs, β-DBE-DBCH showed the highest DFs and concentrations in both human
344 milk groups (Table 1). To our knowledge, this is the first report of β-DBE-DBCH in human milk
345 samples worldwide. Sahlström et al. (2015) detected only α-DBE-DBCH in two pooled breast
346 milk samples in Sweden, at an average of 4.0 pg/g ww, well below the average concentrations
347 detected in our study (41 and 24 pg/g ww in human milk group 1 and group 2, respectively). In
348 line with our results in food items of animal origin, the values of $f_{\beta\text{-DBE-DBCH}}$ ranged from 0.9 to
349 608 across both human milk groups, with a median of 9.6. This exceeds significantly those in
350 UK indoor air (0.53-1.0) and dust (0.32-2.88) ($p < 0.001$) indicating potential isomer-specific
351 degradation/metabolism and/or bioisomerisation in humans. Of note, $f_{\beta\text{-DBE-DBCH}}$ values in human
352 milk were statistically indistinguishable from those in diet samples ($p > 0.05$) indicating the
353 relatively higher abundance of β-DBE-DBCH compared to α-DBE-DBCH in human milk may
354 be at least partially attributable to dietary intake of DBE-DBCH.

355 Despite the ubiquity of EFRs in the environment, very few studies have reported on their levels
356 in human tissues. In Canada, the reported concentrations of EH-TBB (nd-24 ng/g lw) in human
357 milk samples (n=105) (Zhou et al., 2014) exceeded those in our study, while concentrations of
358 BEH-TEBP (nd-6.6 ng/g lw) and DBDPE (nd-25 ng/g lw) were comparable to those reported
359 here (Table 2). Of note, our concentrations of EH-TBB and BEH-TEBP in UK human milk were
360 much lower than those detected in human hair, fingernails and toenails (EH-TBB: 7.6-4540 ng/g;
361 BEH-TEBP: 13-2600 ng/g) as well as serum samples (TBB: 1.3-54 ng/g lw; BEH-TEBP: 19-69

362 ng/g) from the USA (Liu et al., 2016).

363 *LFRs*

364 Concentrations of Σtri-hexa-BDEs, BDE-209 and ΣHBCDDs in human milk group 1 and 2 are
365 summarised in Table 2, with those for individual HBCDD diastereomers summarised in Table S6.
366 Concentrations of ∑HBCDDs in human milk group 2 samples ranged between 0.7-7.1 ng/g lw,
367 which were slightly - albeit not statistically significantly - lower than those in UK human milk
368 group 1 (1.0-22.4 ng/g lw) (Abdallah and Harrad, 2011). While concentrations of ΣHBCDD in
369 food samples in this study were comparable to those in two previous UK studies (Driffield et al.,
370 2008; UK Food Standards Agency, 2006), ΣHBCDDs in UK indoor air and dust collected
371 between 2013 and 2015 appear lower than in samples collected between 2006 and 2007. This
372 may account for the slight downward trend we observed for ΣHBCDDs in UK human milk.

373 The average concentration of Σtri-hexa-BDEs in group 2 (6.5 ng/g lw) is comparable to that
374 reported for group 1 (5.9 ng/g lw) and for Australian human milk samples (7.6 ng/g lw) collected
375 in 2007 (Toms et al., 2009). The relatively higher concentrations of BDE 153 compared to BDE
376 99 in this study concur with several previous studies (Abdallah and Harrad, 2014; Dunn et al.,
377 2010; Frederiksen et al., 2009; Hassine et al., 2012). By comparison, in UK indoor air, dust (Tao
378 et al., 2016) and diet samples (Table S5), concentrations of BDE 153 are exceeded substantially
379 by those of BDE 99, indicating that external exposures through indoor air, dust and diet cannot
380 account for the elevated abundance of BDE 153 in human milk. This higher relative abundance
381 in humans of BDE-153 is more likely attributable to its higher bioaccumulation potential in
382 lipids (as evidenced by a half-life of 6.5 years compared to 1.8 and 2.9 years for BDE-47 and
383 BDE-99 respectively) and/or possible debromination of BDE 209 to BDE 153 (Abdallah and

384 Harrad, 2014), consistent with the significant correlation between concentrations in human milk
385 of BDE 153 and BDE 209 in this study ($p < 0.05$).

386 No significant differences were observed between concentrations of Σtri-hexa BDEs in human
387 milk group 2 (collected in 2014-2015) and group 1 (collected in 2010) (Abdallah and Harrad,
388 2014) ($p > 0.05$) (Table S7). This is in agreement with previous studies reporting no significant
389 change in concentrations of ΣPBDEs (*N.B.* BDE 209 not measured) in human milk samples
390 collected between 2002 and 2007 in Spain (Schuhmacher et al., 2009) and between 2000 to 2009
391 in Taiwan (Shy et al., 2012). Similarly, concentrations of PBDEs in Canadian human milk
392 appear to have stabilised between 2002 and 2005 (Ryan and Rawn, 2014). As diet and dust have
393 been identified as the major pathways of human exposure to PBDEs (Harrad et al., 2008, 2004;
394 Lorber, 2008), it is intriguing that while concentrations of Σtri-hexa BDEs in our UK food
395 samples exceed those reported in two previous UK food surveys (Figure S4); no significant
396 temporal change was observed in concentrations of Σtri-hexa BDEs in UK dust over the studied
397 period (Tao et al., 2016) (2006-2007 to 2013-2015). These contrasting temporal trends in
398 concentrations of tri-hexa BDEs in UK diet and dust are not inconsistent with the hypothesis of
399 Harrad and Diamond (2006) that dietary exposure to chemicals with substantial indoor sources
400 (e.g. FRs) may continue to increase for some time after exposure via indoor pathways has
401 stabilised or fallen as a result of legislative curbs on use. Thus the steady concentrations of tri-
402 hexa-BDEs in human milk observed here may indicate the importance of dust relative to diet as a
403 vector of exposure of the UK population to these contaminants. Concentrations of BDE 209 in
404 human milk group 2 are indistinguishable from those in group 1 (Abdallah and Harrad, 2014) (p
405 > 0.05) (Table 2). This is consistent with the studies of Fängström et al. (2008) and Shy et al.
406 (2012) who also observed no time trend for BDE 209 in human milk samples in Sweden

(between 1980-2004) and Taiwan (between 2000-2009). Consistent with this, no substantial differences were found between BDE 209 concentrations in food in the present study and those in two previous UK dietary studies (Figure S3) (UK Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009). In contrast, concentrations of BDE 209 in UK office dust decreased significantly over the period (2006-2007 to 2013-2015) (Harrad et al., 2008; Tao et al., 2016). Notwithstanding the relatively small number of samples in the current study, this implies that concentrations of this congener in dust exert a relatively minor influence on body burdens. This may be attributable to the very low bioaccessibility from dust (7-14 %) of BDE 209, combined with its very short human half-life (7 days) and preferential partitioning to serum rather than milk fat (Abdallah and Harrad, 2014).

Relative abundance of various FRs

β-DBE-DBCH, BDE 47 and BDE 99 were the major target compounds in meat, fish, egg and dairy products, contributing 59 %, 57 % and 60 % to ΣFRs in these food groups, respectively. In liver samples, β-DBE-DBCH was the predominant flame retardant, accounting for 69 % of ∑FRs. As shown in Figure S5, PBDEs were the predominant FR class found in meat, fish, egg and dairy products, contributing 44 %, 46 % and 52 % of ΣFRs, respectively. In contrast, EFRs were more prevalent in liver samples, accounting for 81 % of ∑FRs.

BDE47 was the most abundant compound in human milk, contributing 20 % of ΣFRs, followed by α-HBCDD and β-DBE-DBCH accounting for 17 % and 11 % of ΣFRs, respectively. PBDEs were the predominant FR class in human milk (Figure S6), contributing an average of 50 % to ΣFRs, followed by EFRs (38 % of ΣFRs). Despite the bans and restrictions on the use of PBDE commercial products, PBDEs remain the most abundant class out of our target FRs in human

429 milk, which may reflect ongoing emissions of these LFRs from old furniture and appliances as
430 well as long half-lives of some PBDE congeners (e.g. BDE 153) in human tissues.

431 **Estimation of dietary intakes**

432 *EFRs*

433 The estimated high-end and average dietary intakes of ∑EFRs in the UK were 26 and 89 ng/day
434 (2.6 and 1.3 ng /body weight/day) for toddlers and adults, respectively (Table S9). The estimated
435 high-end intakes were one order of magnitude higher than the average dietary intakes for both
436 toddlers and adults (Table S9). The main contributor to human dietary exposure to most EFRs
437 and ∑EFRs was meat, followed by fish. However, consumption of eggs and dairy products was
438 the principal contributor to dietary intakes of BEH-TEBP for both toddlers and adults (Figure
439 S7). This is the first estimate of dietary exposure to EFRs for the UK. Furthermore, very limited
440 information on human dietary exposure to EFRs has been reported anywhere to date. Estimated
441 dietary intakes of EFRs for adults and children from an e-waste recycling area in eastern China
442 were 756 and 1827 ng/day, respectively, which is much higher than those in our study (Labunska
443 et al., 2015).

444 β-DBE-DBCH showed the highest contribution to the estimated ∑EFRs intakes in the present
445 study for both adults and children (14 and 50 ng/day respectively). We are aware of a Swedish
446 study on dietary exposure to EFRs in which EFRs were only detected in fish (Sahlström et al.,
447 2015). The estimated median daily intakes of EFRs were 6.8 and 3.3 ng/day for Swedish mothers
448 and toddlers, which is similar to our estimated daily intakes of EFRs through fish consumption
449 (10 and 2.2 ng/day, respectively).

LFRs

Tables S10 and S11 show the estimated intakes of ∑PBDEs via consumption of food in the UK and other different countries. An important caveat is that our estimates of dietary exposure are based on a limited range of food categories and a relatively small number of food items. Estimated average daily intakes of ∑PBDEs in our study are 42 and 124 ng/day for toddlers and adults, respectively, which is lower than one previous study by the UK Food Standards Agency (2006). This is comparable to estimates of dietary PBDE intake in Spain (Domingo et al., 2008) but exceeds those for the USA (Schecter et al., 2009), Belgium (Voorspoels et al., 2007), the Netherlands (Bakker et al., 2008), Sweden (Törnkvist et al., 2011), China (Su et al., 2012) and Romania (Dirtu and Covaci, 2010). Notably, estimated high-end intakes of ∑PBDEs were 5 times higher than the mean dietary intakes for both toddlers and adults (Table S10). Meat was the main source of PBDEs for both toddlers and adults in this study, contributing > 58% of the overall intake, consistent with previous studies conducted in China (Su et al., 2012) and Romania (Dirtu and Covaci, 2010). However, fish was the predominant contributor to human exposure of PBDEs in several other countries such as Sweden (Törnkvist et al., 2011), Belgium (Voorspoels et al., 2007), and Spain (Domingo et al., 2008).

Estimated average daily dietary intakes of ∑HBCDDs for UK adults and toddlers are 8.8 and 31 ng/day respectively (Table S12). Compared with other countries, our estimate of UK adult dietary intake of HBCDDs is comparable to those for the USA (Schecter et al., 2009), Sweden (Törnkvist et al., 2011) and China (Shi et al., 2009); but lower than those in one previous UK study (UK Food Standards Agency, 2006), Belgium (Goscinny et al., 2011), Spain (Eljarrat et al., 2014), the Netherlands (de Winter-Sorkina, 2003) and Romania (Dirtu and Covaci, 2010) (Table S13). Meat was the food group making the greatest contribution to dietary exposure to

ΣHBCDDs (76 % and 73 % for toddlers and adults respectively), followed by fish (23 % and 20 % for toddlers and adults respectively). Elsewhere, meat was the main contributor to dietary exposure in the USA (Schecter et al., 2009), Belgium (Goscinny et al., 2011), Netherlands (de Winter-Sorkina, 2003), China (Shi et al., 2009) and Romania (Dirtu and Covaci, 2010). In contrast, milk and fruit were the main contributors to dietary exposure to HBCDDs in a previous UK study (UK Food Standards Agency, 2006), while in Spain (Eljarrat et al., 2014) and Sweden (Törnkvist et al., 2011), fish was the main source of dietary intake of HBCDDs.

Nursing infants' dietary intake of FRs via breast milk

Table S14 and S15 summarise estimated intakes of target FRs via breast milk for a 1 month old infant (Further details are provided in the SI section). Estimated median dietary exposure to ΣEFRs of a breast-fed infant assuming ingestion of milk from group 2 was 18 ng/kg bw/day, thereby exceeding substantially our estimated average dietary intakes for both UK adults (1.1 ng/kg bw/day for 70 kg adults) and toddlers (2 ng/kg bw/day for 10 kg toddlers). Shi et al. (2016) reported an average ΣEFRs intake of 38.4 ng/kg bw/day for nursing infants in China, which is higher than our estimate. In Shi et al. (2016)'s study, the dietary intake of DBDPE was predominant, accounting for 87 % to 99 % of the total dietary intake of ΣEFRs, while in our study β-DBE-DBCH was the main contributor, with a contribution of 39 % to the total dietary intake of ΣEFRs. The estimated dietary intakes of target EFRs from human milk group 1 were comparable to those from group 2. The dietary intakes of nursing infants of PBDEs and HBCDDs were previously reported using group 1 (collected in 2010) data (Abdallah and Harrad, 2014, 2011) and no substantial differences were observed between those and our estimates from group 2 data (collected in 2014-15).

Relationship between FR intake and human body burdens

To examine the relationship between estimated intakes via various pathways and human body burdens measured in human milk samples; a simple one-compartment, first order pharmacokinetic (PK) model was used (Abdallah and Harrad, 2011). Detailed information about the PK model and methods via which our predicted body burdens are derived are supplied in the SI section.

Despite limited information on the toxicokinetics of EH-TBB and BEH-TEBP in rodents (Knudsen et al., 2016; 2017), to the best of our knowledge, no information is available for bioavailable fractions and human half-lives of EFRs. We therefore estimated these parameters for EFRs from those for related PBDEs (Table S16), e.g. those for DBE-DBCH (4 x Br; molecular weight: 427.8) were assumed equivalent to that for BDE 47 (4 x Br; molecular weight: 485.79).

To our knowledge, this is the first attempt to model the body burden of EFRs in human milk. In general, predicted adult body burdens agreed well with observed levels in human milk (Table 3). Results revealed dietary exposure was the main contributor to UK adult body burdens of DBE-DBCH and EH-TBB (64 %-73 %), while dust ingestion plays a more important role in driving body burdens of BTBPE, BEH-TEBP, and DBDPE (61 %-83 % of body burden) in UK adults. While human exposure to DBDPE via air and dust is relatively high, the low body burdens observed for this EFR suggest low bioaccessibility and/or high biotransformation potential of DBDPE as shown elsewhere for rats (Hakk et al., 2004; Nomeir et al., 1993;Verreault et al., 2007; Wang et al., 2010) and chickens (Zheng et al., 2015). As our predicted body burdens were based on assumed half-lives and absorption efficiencies of EFRs extrapolated from known values

517 for PBDEs, this good agreement indicates our target EFRs likely possess similar
518 physicochemical properties to PBDEs.

519 Overall, good agreement was observed between predicted and observed body burdens for our
520 target EFRs. This was achieved notwithstanding the simplicity of the PK model used, the
521 omission of dermal exposure, and for EFRs a number of additional factors such as: the scarcity
522 of information about crucial parameters like the half-lives of target compounds in human tissues,
523 and uncertainties about the bioaccessibility of target chemicals. While this suggests that we have
524 identified the principal exposure pathways to the target FRs, more research is needed to better
525 characterise exposure and factors that influence the relationship between external exposure and
526 body burdens for EFRs.

527 **Relationship between LFR intake and human body burdens**

528 Generally, predicted body burdens appear reasonably close to measured values of PBDEs in
529 human milk in the present study (Table S17). In a previous report, good agreement was also
530 observed between the predicted body burdens through diet, air and dust and the observed levels
531 of the main target PBDEs in UK human milk (Abdallah and Harrad, 2014). In this study, dietary
532 intake was the major exposure pathway contributing to PBDE body burdens (56 %-85 % for tri-
533 hexa BDEs) in the UK population except for BDE 209 - for which dust ingestion accounted for
534 ~90 of overall body burden.

535 For HBCDDs, predicted body burdens were lower than observed levels for individual HBCDDs
536 in UK human milk when using our estimated dietary intake values of HBCDDs (Table S19).
537 This may be attributable to our focus on meat-related food samples in our study as HBCDD
538 concentrations were highest in vegetables, fruit and cows' milk in previous UK studies (Driffield

et al., 2008; UK Food Standards Agency, 2006). As concentrations of ∑HBCDDs in meat-related food samples in this study were comparable to those reported previously (UK Food Standards Agency, 2006), we therefore used estimated dietary intakes from this previous study to predict body burdens. This resulted in closer agreement between predicted and observed body burdens of individual HBCDDs. This indicates the importance of including vegetables, fruits, milk and high water content food samples when monitoring dietary exposure to HBCDDs.

Conclusions

This study reveals the presence of EFRs in various types of UK food and human milk. Meat was the main source of dietary intakes of PBDEs, EFRs and HBCDDs for both toddlers and adults under an average consumer scenario. Estimated dietary exposures to EFRs were comparable to dietary intakes of PBDEs but higher than those of HBCDDs for both toddlers and adults. The most frequently detected compounds were α-DBE-DBCH, β-DBE-DBCH and EH-TBB in human milk. This may be a health concern as some EFRs show similar persistence, bioaccumulation potential and toxicity properties to legacy FRs (Bearr et al., 2010; Ezechiáš et al., 2012; He et al., 2012; Howard and Muir, 2010; Johnson et al., 2013; Khalaf et al., 2009; Pradhan et al., 2013; Saunders et al., 2013; Tomy et al., 2007), exacerbated by likely future increases in use of EFRs due to the banned and restricted use of LFRs (European Court of Justice, 2008; La Guardia et al., 2006; Stockholm Convention, 2009; UNEP, 2014). In spite of recent evidence of significant temporal trends for LFRs in food/indoor dust/air, no temporal changes were observed for LFRs in human milk over the same time period. This suggests that the lag time between changes in use of these chemicals and a response in human body burdens is not insubstantial. We also examined the relationship between our estimated intakes via different pathways and the body burdens using a simple one-compartment PK model. The results of this

showed predicted adult body burdens to be in agreement with observed levels in human milk for all studied FRs. In summary, dust ingestion appears to constitute the major exposure pathway for UK adults to BDE 209, BTBPE, BEH-TEBP, and DBDPE, while dietary exposure was the major exposure pathway contributing to UK body burdens of HBCDDs, tri-hexa BDEs, DBE-DBCH and EH-TBB.

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Supporting Information

Full details of the analytical protocols, QA/QC measurements and human exposure assessment models are provided as supporting information.

584

Tables

Table 1. Average concentrations of FRs in composite food samples from Birmingham, UK (ng/g lw)

	Lipid weight (%)	Water content (%)	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE	∑EFRs	BDE 209	∑tri-hexa BDEs	∑HBCDDs
Detection Frequency (%)	--	--	97%	100%	77%	60%	63%	33%	--	97%	--	--
Meat												
Beef (3[a])	8.0	67	0.89	1.9	0.20	<0.04	0.44	<1.1	4.5	0.46	15	2.7
Lamb (3)	8.0	68	0.62	6.2	0.19	<0.05	0.28	3.5	11	0.28	2.1	0.32
Pork (3)	8.0	66	0.95	4.1	1.4	2.4	0.20	4.6	14	0.42	21	4.6
Chicken (3)	5.0	73	0.58	7.6	0.36	1.3	0.57	<1.5	11	0.63	11	4.5
Liver												
Beef liver (2)	4.0	64	1.6	49	1.6	<0.06	0.69	4.5	57	3.3	32	20
Lamb liver (2)	5.0	65	<0.26	55	0.19	0.35	0.94	7.6	65	0.43	5.5	1.3
Pork liver (1)	5.0	69	1.1	85	0.63	0.24	5.0	1.5	93	0.51	4.7	7.9
Chicken liver (1)	4.0	73	0.72	34	0.66	0.14	5.8	<1.6	42	0.47	3.2	<0.48
Fish												
Salmon (3)	9.0	65	1.3	4.4	0.32	<0.04	<0.1	6.6	13	0.69	40	12
Mackerel (2)	20	49	1.1	4.9	0.22	0.17	<0.2	<0.63	7.0	0.74	13	3.6
Tuna (2)	2.0	75	0.48	39	0.38	0.78	0.42	21	62	1.7	16	16
Trout (2)	10	67	0.60	4.6	0.43	0.16	1.1	<0.88	7.4	0.34	27	8.8
Egg and dairy products												
Cheese (2)	18	46	0.44	0.99	0.11	0.20	0.22	<0.74	2.3	0.21	5.1	<0.24
Hen Eggs (1)	11	51	0.42	3.0	0.10	0.18	1.8	<1.2	6.1	0.53	1.9	1.3

[a]Number in parentheses denotes number of composite samples of that food group analysed.

588 **Table 2. Descriptive statistics for concentrations for EFRs and LFRs in UK human milk (ng/g lw) [a]**

	Lipid weight (%)	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE	∑EFRs	Σtri-hexa BDEs	BDE 209	∑HBCDDs
Human milk collected in 2010 (n=25)											
Detection Frequency	--	20%	76%	44%	28%	36%	4%	--	--	69%	--
Mean	3.2	--	6.8	--	--	--	--	--	5.9	0.31	5.95
Median	3.5	<0.13	3.1	<0.01	<0.1	<0.1	<0.78	7.9	5.00	0.25	3.83
Minimum	1.9	<0.13	<0.13	<0.01	<0.1	<0.1	<0.78	0.57	0.20	<0.06	1.04
Maximum	4.4	1.7	38	2.1	56	4.6	250	260	26.10	0.92	22.37
Human milk collected in 2014-2015 (n=10)											
Detection Frequency	--	100%	100%	90%	40%	50%	10%	--	--	40%	--
Mean	3.9	0.67	2.5	0.21	--	0.25	--	--	6.5	<0.22	3.2
Median	4.1	0.60	1.2	0.16	<0.1	<0.1	<0.78	3.1	5.8	<0.22	2.9
Minimum	1.5	0.30	0.43	<0.01	<0.1	<0.1	<0.78	1.9	1.7	<0.22	0.69
Maximum	5.3	1.1	10	0.48	0.71	0.73	58	59	14	0.67	7.1

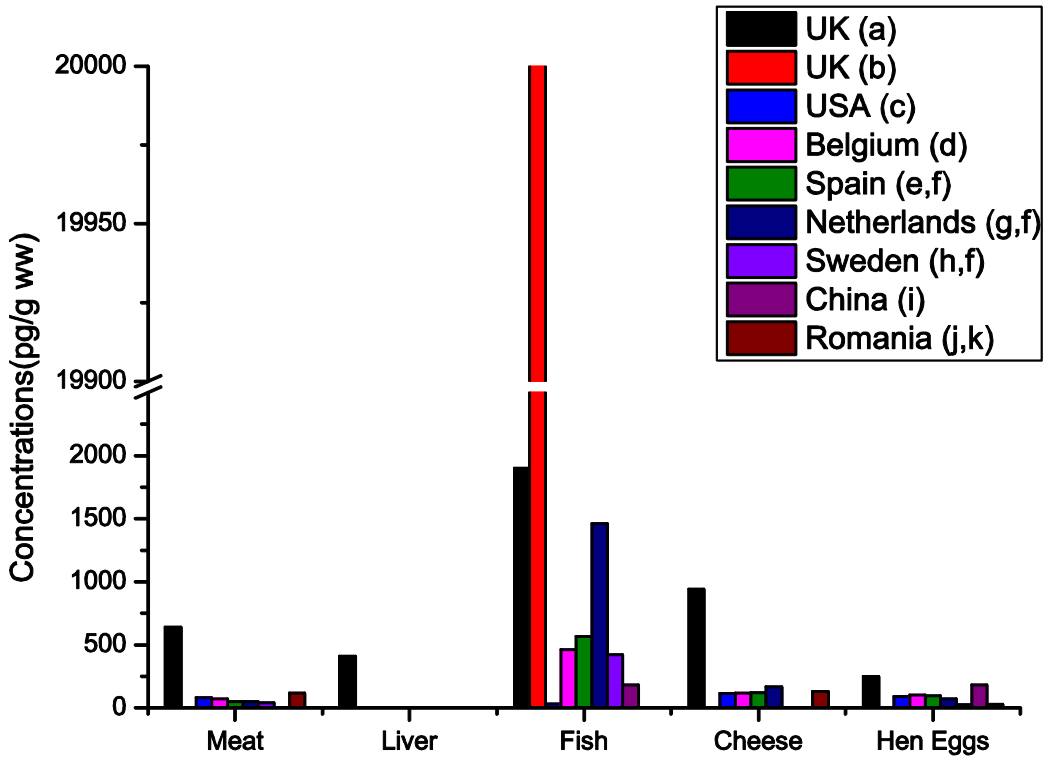
589 [a] Average concentrations were calculated only for those FRs for which detection frequency>50%.

Table 3. Estimated median and average daily intakes[a] of selected target EFRs and comparison of resultant predicted adult body burdens[b] with those observed in human milk

Exposure Pathway/EFR	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE
Average intake (ng/day)						
Dust[c]	0.26	0.30	0.97	21.00	14.00	20.00
Diet[d]	8.20	49.84	3.34	5.79	6.04	15.71
Air[c]	2.30	1.70	0.17	0.31	0.17	0.44
Median intake (ng/day)						
Dust[c]	0.16	0.18	0.19	1.50	2.60	6.50
Diet[d]	7.72	49.59	3.48	4.19	6.75	9.53
Air[c]	1.70	1.20	0.05	0.13	0.04	0.10
Average predicted body burdens (ng/g lw)						
Dust	0.01	0.02	0.04	0.15	0.10	0.003
Diet	0.43	2.61	0.15	0.04	0.04	0.003
Air	0.21	0.15	0.02	0.002	0.001	0.001
Sum	0.65	2.78	0.21	0.19	0.14	0.01
Median predicted body burdens (ng/g lw)						
Dust	0.01	0.01	0.01	0.01	0.02	0.001
Diet	0.40	2.60	0.16	0.03	0.05	0.002
Air	0.15	0.11	0.005	0.001	0.0003	0.0001
Sum	0.57	2.72	0.17	0.04	0.07	0.003
Observed body burdens (ng/g lw)						
Average	0.67	2.50	0.21	0.15	0.25	--
Median	0.60	1.20	0.16	<0.1	<0.1	<0.78

[a]Values below LOQ were assumed to be 1/2 LOQ. Average and median dust intakes based on assumption that 20 mg/day dust ingested (Jones-Otazo et al., 2005) containing the average and median FR concentrations reported for UK house dust and average inhalation rate of 20 m^3/day (Currado and Harrad, 1998);
[b]Body burdens were calculated only for those FRs for which detection frequency>50%;
[c]Data from Tao et al. (2016);
[d]Estimated from the average consumption rates calculated for each food group (Food Standards Agency, 2014), the average and median FRs concentrations in this study were used for calculation of average and median dietary intakes, separately.

599 **Figure 1. Average concentrations of ∑PBDEs (pg/g ww) in food samples from different countries.**



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601 a) data from this study; b) date from Rose et al.(2015); c) data from Schecter et al.(2009); d) data from Voorspoels et al.(2007); e)
602 data from Domingo et al.(2008); f) BDE 209 was not measured; g) data from Bakker et al.(2008); h) data from Törnkvist et
603 al.(2011); i) data from Su et al.(2012); j) data from Dirtu and Covaci(2010); k) median concentrations of ∑PBDEs.

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Abstract

The legacy flame retardants (LFRs) polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD), together with six emerging flame retardants (EFRs) were measured in United Kingdom (UK) human milk collected in 2010 (n=25) and 2014-15 (n=10). These data are the first report of the presence of EFRs in UK human milk. The most abundant EFR was β-tetrabromoethylcyclohexane (DBE-DBCH) (average = 2.5 ng/g lw; geometric mean = 1.5 ng/g lw), which is comparable to the concentrations of the most abundant LFRs i.e. BDE 47 and α-HBCDD at 2.8 and 2.1 ng/g lw, respectively (geometric mean = 2.1 and 1.7). The estimated average dietary intake of ΣEFRs by UK nursing infants was 18 ng/kg bw/day. EFRs were also measured in UK foodstuffs with β-DBE-DBCH again the predominant compound detected, accounting – on average – for 64.5±23.4% of ΣEFRs. Average estimated dietary intakes of ∑EFRs in the UK were 89 and 26 ng/day (1.3 and 2.6 ng /body weight/day) for adults and toddlers, respectively. Concentrations of Σtri-hexa BDEs in our UK food samples exceeded those reported in UK samples from the same food categories collected in 2003-04 and 2006. Despite this and our recent report elsewhere of significant temporal declines in concentrations of BDE 209 in UK indoor dust ($p < 0.05$) and HBCDDs in UK indoor dust and air ($p < 0.001$), no significant temporal differences ($p > 0.05$) were observed between concentrations of Σtri-hexa BDEs, BDE 209 and HBCDDs in human milk sampled in 2010 and those obtained in 2014-15. UK adult body burdens for EFRs were predicted via inhalation, diet and dust ingestion using a simple pharmacokinetic model. The predicted EFR body burdens compared well with observed concentrations in human milk.

Supporting information for

Emerging and legacy flame retardants in UK indoor air and dust: evidence for replacement of PBDEs by emerging flame retardants?

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17 Tables, 4 figures and method description.

1. Sampling methods

The water content of each food sample was determined gravimetrically to permit calculation of concentrations on a wet weight (ww) basis. Concentrations of FRs (ng/g ww) in each food sample were multiplied by the sample mass to calculate an estimate of dietary intake.

2. Analytical protocols of HBCDDs

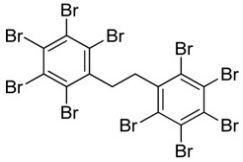
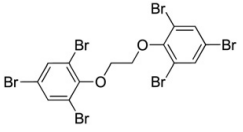
Analysis of three HBCDD diastereomers (α, β, and γ-HBCDDs) was achieved using a dual pump Shimadzu LC-20AB Prominence high pressure liquid chromatograph (Shimadzu, Kyoto, Japan) equipped with a Sciex API 2000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA, USA). A Varian Pursuit XRS3 (Varian, Inc., Palo Alto, CA, USA) C18 reversed phase analytical column (150 mm × 2 mm i.d., 3 μm particle size) were used for separation of α-, β-, and γ-HBCDDs. The following mobile phase program was used: (a) 1:1 methanol/water and (b) methanol at a flow rate of 180 μL min-1 was applied; the mobile phase b starts at 50% before increasing linearly to 100% over 4 min, held for 5 min followed by a linear decrease to 88% over 1 min, and a rapid drop to 50%, held for 1 min. Post-elution was conducted by increasing the mobile phase b gradually to 100% over 1 min, held 6 min, and then finished to 50% for 4 min. Using this method, α-, β-, and γ-HBCDDs were separated at the retention times of 9.0, 10.6, and 11.2 minutes respectively.

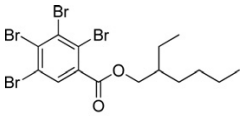
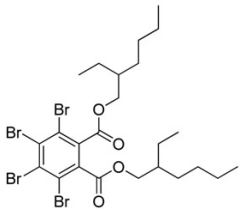
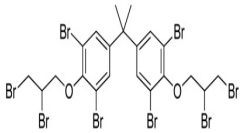
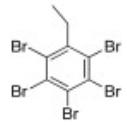
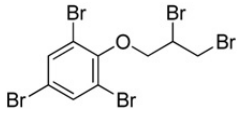
Table S1: Linear ranges, R^2, qualifier/quantifier ions, internal standard (IS), LODs, and LOQs for PBDEs, HBCDDs and EFRs

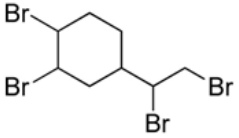
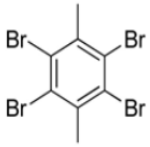
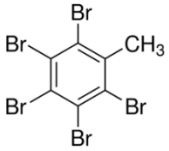
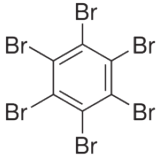
	Linear ranges (pg/uL)	R^2	quantifier/ qualifier ions* (m/z)	IS	LOD (pg/uL)	Diet and Human milk LOQ (ng/g dry weight)
α-DBE-DBCH	25-500	0.9991	79/81	BDE77	0.070	0.04
β-DBE-DBCH	25-500	0.9992	79/81		0.070	0.04
EH-TBB	25-500	0.9989	356.8/358.8		0.004	0.003
BTBPE	25-500	0.9987	330.8/332.8	^{13}C-BTBPE	0.046	0.03
BEH-TEBP	25-500	0.9991	463.7/383.7	^{13}C-BEH-TEBP	0.004	0.003
DBDPE	50-1000	0.9988	79/81	^{13}C-BDE209	0.44	0.25
BDE28	25-500	0.9993	81/326.9	BDE77	0.011	0.01
BDE47	25-500	0.9995	81/326.9		0.014	0.01
BDE100	25-500	0.9986	81/403.9		0.004	0.003
BDE99	25-500	0.9991	81/403.9		0.004	0.003
BDE154	25-500	0.9986	81/483.8	BDE128	0.021	0.01
BDE153	25-500	0.9988	81/483.8		0.018	0.01
BDE183	25-500	0.9976	81/483.8		0.046	0.03
BDE209	50-1000	0.9985	486.8/484.8	^{13}C-BDE209	0.12	0.07
α-HBCDD	25-500	0.9987	640.9/79.0	^{13}C-α-HBCDD	0.056	0.03
β-HBCDD	25-500	0.9986	640.9/79.0	^{13}C-β-HBCDD	0.049	0.03
γ-HBCDD	25-500	0.9991	640.9/79.0	^{13}C-γ-HBCDD	0.039	0.02

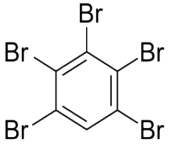
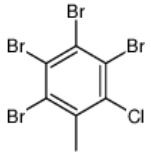
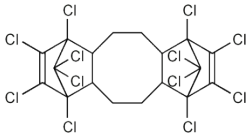
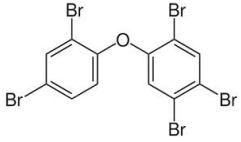
* MS/MS detection operated in the multiple reaction monitoring (MRM) mode was used for quantitative determination of HBCDDs.

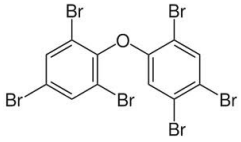
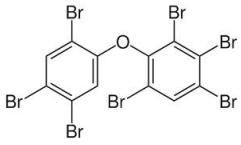
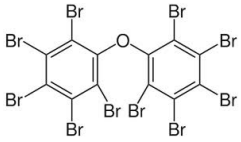
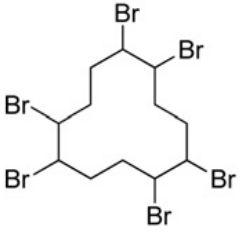
49 **Table S2: Physicochemical properties of some important EFRs, PBDEs and HBCDDs**

Compound	Acronym	Chemical structure	Molecular formula	Molecular weight	Melting point(°C)	Boiling point(°C)	Vapour pressure (Pa) (25 °C)	Water solubility (g/L) (25 °C)	Log K_{OW}	-Log K_{OA}	Half-life in air (hours)	Half-life in water (hours)	Half-life in soil (hours)	Production volume	Type of BFR
Decabromodiphenyl ethane	DBDPE		$C_{14}H_4Br_{10}$	971.2[a]	334-337[b], 344-349[d], 348-353[e], 351-355[e]	676±50[a]	6.0E-15 [a] 1.0E-06 [e]	2.10E-07 [a] 7.2E-04 [e]	11.1 [a]	18.8 [l] 19.34 [o]	53.6 [l]	4320 [l]	8640 [l]	N/A	Additive [g]
1,2-bis(2,4,6-tribromophenoxy)ethane	BTBPE		$C_{14}H_8Br_6O_2$	687.6 [a]	N/A	566.4±50.0[a]	3.88E-10[a]	1.90E-05 [a]	7.88±0.86 [a]	15.0 [l]	8.6 [l]	4320 [l]	8640 [l]	LPV [g]	Additive [g]

2-ethylhexyl-2,3,4,5-tetrabromobenzoate	EH-TBB (TBB)		$C_{15}H_{18}Br_4O_2$	549.9[c]	N/A	N/A	3.71E-07 [e]	1.14E-05 [f]	7.73 [c] 8.75 [f]	12.34 [q]	N/A	N/A	N/A	N/A	Additive [g]
Bis(2-ethylhexyl) tetrabromophthalate	BEH-TEBP (TBPH)		$C_{24}H_{34}Br_4O_4$	706.1 [a]	N/A	584.8±45.0[a]	1.55E-11 [a]	1.60E-06 [a]	10.08±0.94 [a]	17.7 [l] 16.86 [o]	5.9 [l]	1440 [l]	2880 [l]	LPV [g]	Additive [g]
Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)	TBBPA-DBDPE (TBBPA-DBPE)		$C_{21}H_{20}Br_8O_2$	943.6 [a]	90-105 [b], 90-100 [c]	676.5±55.0[a]	1.60E-07 [a]	1.60E-07 [a]	10.42±0.7 [a]	21.1 [l]	12.2 [l]	4320 [l]	8640 [l]	LPV [g]	Additive [g]
Pentabromoethylbenzene	PBEB		$C_8H_5Br_5$	500.7 [a]	138 [b]	413.3±40.0[a]	3.2E-04 [a] 4.67E-05[e]	3.50E-04 [a]	6.40±0.62 [a]	9.9 [l]	111.6 [l]	4320 [l]	8640 [l]	LPV [g]	Additive [g]
2,3-dibromopropyl 2,4,6-tribromophenyl ether	TBP-DBPE (DPTE)		$C_9H_7Br_5O$	530.6 [c]	N/A	N/A	1.86E-05 [c]	N/A	5.82 [c]	N/A	N/A	N/A	N/A	N/A	Additive [c]

Tetrabromoethylcyclohexane	DBE-DBCH (TBECH)		$C_8H_{12}Br_4$	427.8 [c]	N/A	N/A	2.97E-03 [c] 1.05E-04 [e]	6.92E-05 [e]	4.82 [c], 5.24 [e], 5.25 [p]	8.01 [p]	52.8 [m]	756864 (pH=7) [m]	N/A	N/A	Additive [g]
Benzene, 1,2,4,5-tetrabromo- 3,6-dimethyl	TBX (p-TBX)		$C_8H_6Br_4$	421.75 [c]	N/A	N/A	5.80E-03 [c]	N/A	6.2 [c]	8.81 [t]	N/A	N/A	N/A	N/A	Additive [c]
Pentabromotoluene	PBT		C7H3Br5	486.6 [g]	280-282 [g], 288-289 [g]	394.4±37 [g]	1.22E-03 [g]	7.80-E04 [g]	5.87±0.62 [g], 5.43 [g], 6.99 [t], 6.26 [c]	9.66 [u]	N/A	N/A	N/A	LPV [g]	Additive [c]
Hexabromobenzene	HBB		C6Br6	551.5 [g]	327 [g], 326 [g]	417.5±40 [g]	1.14E-04 [g] 3.17E-04 [g]	7.70E-04 [g], 1.10E-07 [g]	5.85±0.67 [g], 6.07 [g]	10.26 [u]	1992 [n]	7584 [n]	7584 [n]	N/A	Additive [c]

pentabromobenzene	PBBz		C6HBr5	472.59	N/A	N/A	N/A	N/A	6.44 [t]	9.10 [t]	N/A	N/A	N/A	N/A	N/A
Tetrabromo-o-chlorotoluene	TBCT (TBoCT)		C7H3Br4Cl	442.17 [c]	N/A	N/A	1.72E-03 [c]	N/A	6.29 [c]	8.82 [t]	N/A	N/A	N/A	N/A	Additive [c]
dechlorane plus	DDC-CO (DP)		C18H12Cl12	653.7 [v]	206 [w], 350 °C with decompos -ition [v]	N/A	1.37E-11 [c], 4.71E-08 [w]	4.0E-11 [w]	9.3 [v], 10.12 [c], 11.27 [p]	13.1 [t]	N/A	N/A	N/A	N/A	Additive [c]
2,2',4,4',5-Pentabromodiphenyl ether	BDE 99		$C_{12}H_5Br_5O$	564.69	90.5-94.5	434.2	1.32E-07 [h]	9E-06 [h]	7.32 [h]	11.31 [r]	456 [n]	19992 [n]	19992 [n]	HPV [j]	Additive

2,2',4,4',5,6'- Hexabromodiphenyl ether	BDE 154		$C_{12}H_4Br_6O$	643.58	N/A	453.2	2.85E-08 [h]	1E-06 [h]	7.82 [h]	11.92 [r]	N/A	N/A	N/A	HPV [j]	Additive
2,2',3,4,4',5',6- Heptabromodiphenyl ether	BDE 183		$C_{12}H_3Br_7O$	722.48	N/A	490.7	3.51E-09 [h]	2E-06 [h]	8.27 [h]	11.96 [r]	1536 [m]	N/A	N/A	HPV [k]	Additive
Decabromodiphenyl ether	BDE 209		$C_{12}Br_{10}O$	959.17 [h]	300-310 [h]	decomposes at >320	4.63E-06(21°C) [h]	<1E-07 [h]	8.70 [i]	18.42 [t], 14.98 [s]	7632 [m]	N/A	N/A	HPV	Additive
Hexabromocyclodecane	HBCDD		$C_{12}H_6Br_6$	641.7 [c]	N/A	decomposes at >190 [c]	1.04E-07 [c]	N/A	7.92 [c]	11.8 [o]	40.8 [m]	1.05E-15 (pH=7) [m]	N/A	HPV	Additive [c]

a) Data from SciFinder originating from calculated properties (ACD/labs Software V9.04); b) Data from SciFinder data base originating from experimentally determined properties; c) Data from Bergman et al., (2012); d) Experimental data from Li et al. (2004); e) Experimental data from the Environment Agency Dungey, S and Akintoye (2007); e) Data from Syracuse Research Corporation. f) Data from US. EPA (2008a); (g) Information from Covaci et al., (2011); (h) Data from US. EPA (2008b); i) Data from Sifleet (2009); j) Data from Penta-BDE(Alaee et al. (2003)); k) Data from from octa-BDE (Alaee et al. (2003)); l) Data from NPCA (2008); m): Data from Nyholm (2009); n) Data from Wegmann et al. (2009); o) Data from Ruan et al. (2009); p) Data from Howard and Muir (2010); q): Data from Stapleton et al. (2008); r) Data from Harner and Shoeib (2002); s) Data from Cetin and Odabasi (2008); t) Data from HENRYWIN v3.20 (EPIWIN 4) u) Stenzel et al. (2013); v) Data from Xian et

al. (2011); w) Data from Feo et al. (2012); HPV: high production volume (above 1000 tons/year); LPV: low production volume (below 1000 tons/year); N/A: not available.

Table S3: The recoveries (%) of the EH-TBB and BEH-TEBP in the matrix spiked experiments

	Spiked egg samples		Spiked human milk samples	
	Low levels (0.5 ng, n=3)	High levels (25 ng, n=3)	Low levels (0.5 ng, n=3)	High levels (25 ng, n=3)
EH-TBB	80%	92%	81%	90%
BEH-TEBP	78%	83%	75%	83%

63 **Table S4: Average concentrations of EFRs (ng/g lw) in biota samples from different countries.**

Samples	α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BTBPE	BEH-TEBP	DBDPE	Location	References
Meat								
Meat	0.58-0.95	1.9-7.6	0.19-1.4	<0.04-2.4	0.20-0.57	<1.1-4.6	UK	This study
Beef				0.56		<0.06[c]	UK	(Fernandes et al., 2010)
Pork				0.55		<0.06 [c]		
Lamb				0.05		<0.06 [c]		
Turkey				1.76		<0.06 [c]		
Chicken			2.66	<0.35	1.78	<0.45	Shanghai and Nanjing City, China	(Labunska et al., 2015)
Duck			2.74	1.87	<0.25	<0.45		
Pork			2.14	2.69	1.37	<0.45		
Chicken			24.7	1.46	8.97	<0.45	E-waste area, South China	
Duck			24.2	4.57	7.23	<0.45		
Pork			38.2	5.4	12.4	<0.45		
Liver								
Liver	<0.26-1.6	34-85	0.19-1.6	<0.06-0.35	0.69-5.8	<1.6-7.6	UK	This study
Pork liver				0.81		<0.06 [c]	UK	(Fernandes et al., 2010)
Chicken liver				0.75		<0.06 [c]		
Chicken liver			5	3.38	2.61	<0.45	Shanghai and Nanjing City, China	(Labunska et al., 2015)
Duck liver			8.2	3.27	1.69	<0.45		
Chicken liver			35	15	10.6	<0.45	E-waste area, South China	
Duck liver			38.4	11.7	13.7	<0.45		
Fish								
Fish	0.48-1.3	4.4-39	0.22-0.43	<0.04-0.78	<0.1-1.1	<0.63-21	UK	This study
Salmon				0.26		<0.06 [c]	UK	(Fernandes et al., 2010)
Mackerel				0.3		<0.06 [c]		
Herring				0.25		<0.06 [c]		

Haddock				0.83		<0.06 [c]		
Lemon Sole				3.33		<0.06 [c]		
Whitebait				0.77		<0.06 [c]		
Fish			4	2.1	1.9	<0.45	Shanghai and Nanjing City, China	(Labunska et al., 2015)
Fish			24.7	1.46	8.97	<0.45	E-waste area, South China	
Fish [a]	97	17	<14	1.1-3.6 [b]	< 26		Sweden	(Sahlström et al., 2015)
Fish				<0.05-3.72		<0.1-3.30	Lake Winnipeg, Canada	(Law et al., 2006)
Juvenile common sole				0.08-0.31		0.28-1.13	Nursery zones situated along the French coast	(Munschy et al., 2011)
Fish				<0.012-0.15		<3.8	E-waste area, South China	(Shi et al., 2009)
Fish						<4.9-230	Dongjiang River, South China	(He et al., 2012)
Fish and seafood						121	Shandong Province, North China	(Cao et al., 2015)
Eggs								
Egg	0.42	3.0	0.10	0.18	1.8	<1.2	UK	This study
Chicken eggs			1.73	<0.35	<0.25	<0.45	Shanghai and Nanjing City, China	(Labunska et al., 2015)
Chicken eggs			4.8	2.93	1.16	<0.45	E-waste area, South China	
Duck eggs			1.21	<0.35	<0.25	<0.45	Shanghai and Nanjing City, China	
Duck eggs			4.03	2.11	1.11	<0.45	E-waste area, South China	
Free range organic eggs				0.29		<0.06 [c]	UK	(Fernandes et al., 2010)
Chicken eggs				37.2-264		5.97-37.9	E-waste area, South China	(Zheng et al., 2012)

a) the units are pg/g ww; b) mLOD – mLOQ; c) the units are ng/g ww.

66 **Table S5: Average concentrations (pg/g ww in parentheses) of PBDEs in composite food samples from Birmingham, UK (ng/g lw)**

	Average Lipid weight (%)	Average Water content (%)	BDE 28	BDE 47	BDE 100	BDE 99	BDE 154	BDE 153	BDE 209	∑tri-hexa BDEs	∑PBDEs
DF	--	--	73%	93%	90%	100%	83%	100%	97%	--	--
Meat											
Beef	7.6	67	0.32 (23)	5.5 (360)	1.2 (73)	7.2 (470)	0.42 (27)	0.6 (38)	0.46 (32)	15 (990)	16 (1000)
Lamb	8.0	68	0.082 (7.5)	0.5 (45)	0.48 (36)	0.76 (65)	0.10 (8.3)	0.17 (15)	0.28 (21)	2.1 (177)	2.4 (200)
Pork	8.0	66	0.35 (15)	7.4 (290)	2.0 (82)	9.6 (370)	0.66 (25)	0.88 (33)	0.42 (24)	21 (810)	21 (830)
Chicken	4.6	73	<0.06 (<5.0)	3.5 (160)	1.0 (44)	5.6 (250)	0.43 (19)	0.54 (24)	0.63 (28)	11 (500)	12 (520)
Liver											
Beef liver	4.0	64	0.62 (24)	6.5 (250)	2.0 (76)	20 (760)	1.1 (41)	1.4 (53)	3.3 (120)	32 (1200)	35 (1300)
Lamb liver	5.3	65	<0.18 (<7.8)	0.034 (1.8)	3.9 (160)	0.70 (30)	0.33 (17)	0.41 (21)	0.43 (23)	5.5 (240)	5.9 (260)
Pork liver	4.7	69	0.33 (19)	2.0 (82)	0.17 (5.5)	1.7 (63)	0.14 (6.8)	0.34 (20)	0.51 (23)	4.7 (200)	5.3 (220)
Chicken liver	4.6	73	0.12 (5.5)	1.3 (59)	0.069 (3.0)	1.4 (61)	0.16 (7.2)	0.19 (8.7)	0.47 (21)	3.2 (150)	3.7(170)
Fish											
Salmon	9.1	65	0.8 (61)	17 (1100)	3.9 (230)	15 (720)	1.5 (94)	1.4 (73)	0.69 (41)	40 (2300)	40 (2300)
Mackerel	24	49	0.63 (130)	5.9 (1200)	1.2 (250)	3.8 (770)	1.0 (210)	0.39 (80)	0.74 (150)	13 (2600)	14 (2800)
Tuna	2.0	75	0.43 (8.9)	6.0 (130)	2.6 (54)	3.7 (80)	2.6 (59)	1.2 (26)	1.7 (39)	16 (360)	18 (400)
Trout	9.2	67	0.76 (71)	12 (950)	2.5 (190)	8.6 (550)	2.0 (150)	1.6 (120)	0.34 (32)	27 (2000)	28 (2100)
Egg and dairy product											
Cheese	18	46	0.068 (12)	1.9 (340)	0.59 (100)	2.2 (390)	0.12 (21)	0.14 (26)	0.21 (37)	5.1 (900)	5.3 (940)
Hen Eggs	11	51	<0.04 (<4.9)	0.19 (20)	0.13 (14)	0.3 (32)	1.2 (130)	<0.04 (<4.9)	0.53 (56)	1.9 (200)	2.4 (250)

Table S6: Average concentrations (pg/g ww in parentheses) of HBCDDs in composite food samples from Birmingham, UK (ng/g lw)

	α-HBCDD	β-HBCDD	γ-HBCDD	∑HBCDDs
DF	83%	70%	73%	
Meat				
Beef	1.6 (100)	0.44 (28)	0.62 (40)	2.7 (170)
Lamb	0.22 (15)	<0.12 (<16)	<0.08 (<5.5)	0.32 (26)
Pork	2.6 (120)	0.84 (34)	1.2 (53)	4.6 (200)
Chicken	2.3 (100)	0.91 (40)	1.3 (56)	4.5 (200)
Liver				
Beef liver	7.0 (260)	2.2 (83)	11 (400)	20 (740)
Lamb liver	0.48 (32)	0.26 (17)	0.6 (41)	1.3 (90)
Pork liver	3.3 (110)	0.89 (30)	3.7 (120)	7.9 (270)
Chicken liver	<0.18 (<8.0)	<0.18 (<8.0)	<0.12 (<5.4)	<0.48 (<22)
Fish				
Salmon	7.3 (490)	2.9 (220)	1.7 (120)	12 (830)
Mackerel	2.4 (490)	0.2 (40)	1.0 (210)	3.6 (740)
Tuna	12 (110)	2.2 (50)	1.8 (18)	16 (180)
Trout	6.0 (350)	1.2 (72)	1.6 (90)	8.8 (510)
Egg and dairy products				
Cheese	<0.089 (<7.8)	<0.089 (<8.0)	<0.059 (<5.4)	<0.24 (<43)
Hen Eggs	0.78 (190)	0.28 (68)	0.19 (45)	1.3 (300)

72 **Table S7: Descriptive statistics for concentrations for PBDEs and HBCDDs in UK human milk (ng/g lw)**

	BDE 28	BDE 47	BDE 100	BDE 99	BDE 154	BDE 153	α-HBCDD	β-HBCDD	γ-HBCDD
Archived human milk samples collected in 2010 (n=35) (Abdallah and Harrad, 2014; M. A. Abdallah and Harrad, 2011)									
DFs	--	100%	89%	94%	77%	97%	--	--	--
5th percentile	--	0.27	0.03	0.05	0.03	0.09	1.10	0.09	0.15
95th percentile	--	8.23	0.98	1.7	0.68	3.16	15.27	0.67	2.11
Mean	--	3.3	0.45	0.71	0.30	1.10	4.91	0.32	0.73
Median	--	2.8	0.38	0.69	0.21	0.91	3.71	0.30	0.56
Min	--	0.17	<0.05	<0.06	<0.06	<0.06	0.75	0.08	0.13
Max	--	14.65	1.86	3.43	11.10	4.57	19.71	0.75	2.29
Human milk collected from 2014-2015 (n=10)									
DFs	90%	100%	100%	100%	90%	100%	100%	60%	100%
5th percentile	0.03	0.63	0.08	0.45	0.06	0.62	0.65	<0.10	0.29
95th percentile	0.41	7.0	2.1	1.7	0.21	2.4	3.7	0.46	1.9
Mean	0.19	2.8	0.73	1.0	0.13	1.7	2.1	0.25	0.90
Median	0.14	2.2	0.53	0.77	0.12	1.8	1.9	0.23	0.73
Min	<0.03	0.52	0.07	0.42	<0.03	0.49	0.40	<0.10	0.16
Max	0.41	7.7	2.2	2.0	0.24	2.7	4.4	0.61	2.2

3. Estimation of daily dietary intakes

Consumption rates for each liver (four groups) and each oily fish (four groups) category were derived from the total liver and oily fish consumptions in the survey report divided by 4. (Public Health England and the Food Standards Agency, 2014) The weight of each egg used for calculating daily intakes of FRs via egg consumption was corrected for the corresponding eggshell weight and concentrations on a whole egg basis as reported previously elsewhere (Labunska et al., 2013). It is notable that raw food samples were analysed in our study as preparation and cooking may affect the concentrations of chemicals (Perelló et al., 2009). We assume that exposed adults and toddlers in this study weigh 70 and 10 kg, separately (Abdallah et al., 2008).

Table S8: Average (standard deviation in parentheses) quantities of food consumed by UK toddlers and adults (g/day) (Food Standards Agency, 2014)

	Toddlers [a]	**Adults [b]**
Beef	17 (28)	48 (71)
Lamb	4 .1 (15)	12 (39)
Pork	3.1 (13)	11 (32)
Chicken	14 (21)	61 (77)
Beef liver	0.04 (0.44)	0.34 (2.3)
Lamb liver	0.04 (0.44)	0.34 (2.3)
Pork liver	0.04 (0.44)	0.34 (2.3)
Chicken liver	0.04 (0.44)	0.34 (2.3)
Salmon	0.58 (3.8)	2.7 (7.7)
Mackerel	0.58 (3.8)	2.7 (7.7)

Tuna	0.58 (3.8)	2.7 (7.7)
Trout	0.58 (3.8)	2.7 (7.7)
Cheese	8.6 (9.4)	15 (19)
Hen Eggs	8.5 (14)	20 (38)

a) derived from data of food consumption for age group (1.5-3 years old); b) derived from data of food consumption for age group (19-64 years old).

Table S9: Estimated average and high-end [a] dietary intakes of ∑EFRs (ng/day) for UK adults and toddlers

	Toddlers		Adults	
	Average consumer	**High-end consumer**	**Average consumer**	**High-end consumer**
Meat	18	100	64	294
Liver	0.42	10	3.8	56
Fish	2.4	34	11	76
Cheese	3.6	11	6.3	22
Hen Eggs	1.7	7.3	4.0	19
Total	26	162	89	467

a) estimates of high end intakes were derived from food consumption figures in Table S7 by assuming that a high-end consumer of each food group consume the average quantities of food consumed + 2 × standard deviations (SD). This is because statistically the 95th percentile value equals the average plus 2 × SD.

Table S10: Estimated average and high-end [a] dietary intakes of ∑PBDEs (ng/day) for UK adults and toddlers

	Toddlers		Adults	
	Average consumer	**High-end consumer**	**Average consumer**	**High-end consumer**
Meat	28	135	89	372
Liver	0.08	1.8	0.61	8.9
Fish	4.4	61	20	133
Cheese	8.1	26	14	48
Hen Eggs	0.67	2.9	1.2	5.8
Total	42	227	124	568

a) estimates of high end intakes were derived from food consumption figures in Table S7 by assuming that a high-end consumer of each food group consume the average quantities of food consumed + 2 × standard deviations (SD). This is because statistically the 95th percentile value equals the average plus 2 × SD.

Table S11: Estimated average adult dietary intakes of ∑PBDEs (ng/day) in different countries

Country	Total PBDEs intake (ng/day)	Year	References
UK	124	2015	This study
UK	413	2003-2004	(UK Food Standards Agency, 2006)
UK	107 (90.5 [a])	2006	(Harrad et al., 2004)
USA	50	2009	(Schecter et al., 2009)
Belgium	23-48	2005	(Voorspoels et al., 2007)
Spain	75.4	2006	(Domingo et al., 2008)
Netherlands	55.3	2003-2004	(Bakker et al., 2008)
Sweden	49	2005	(Törnkvist et al., 2011)
China	9.9	2006	(Su et al., 2012)
Romania [a]	40	2007	(Dirtu and Covaci, 2010)

a) Based on median values of PBDEs and consumption of omnivorous diets only.

Table S12: Estimated average and high-end [a] dietary intakes of ∑HBCDDs (ng/day) for UK adults and toddlers

	Toddlers		Adults	
	Average consumers	**High-end consumers**	**Average consumers**	**High-end consumers**
Meat	6.4	30	23	93
Liver	0.04	1.0	0.37	5.5
Fish	1.3	18	6.1	41
Cheese	0.18	0.6	0.32	1.1
Hen Eggs	0.79	3.4	1.9	8.8
Total	8.8	54	31	149

a) estimates of high end intakes were derived from food consumption figures in Table S7 by assuming that a high-end consumer of each food group consumes the average quantities of food consumed + 2 × standard deviations (SD). This is because statistically the 95th percentile value equals average plus 2 × SD.

Table S13: Estimated average dietary intakes of ∑HBCDDs (ng/day) in different countries

Country	Total HBCDDs intake (ng/day)	Year	References
UK	31	2015	This study
UK	413 [a]	2003-2004	(UK Food Standards Agency, 2006)
USA	16	2009	(Schecter et al., 2009)
Belgium [a, b]	69	2006-2007	(Goscinny et al., 2011)
Spain	177	2009	(Eljarrat et al., 2014)
Netherlands	99-191	2002	(de Winter-Sorkina et al., 2013)
Sweden	10.2	2005	(Törnkvist et al., 2011)
	11	2010	(Sahlström et al., 2015)
China	27	2007	(Shi et al., 2009)
Romania [a]	77	2007	(Dirtu and Covaci, 2010)

a) assuming the body weight was 70 kg for daily intake estimation calculation.

Table S14: Estimated exposure [a, b] (ng/kg bw/day) of a 1 month old infant to target FRs via ingestion of breast milk sampled in 2010

	Mean	Median
α-DBE-DBCH	--	0.38
β-DBE-DBCH	40	18
EH-TBB	--	0.29
BTBPE	--	0.29
BEH-TEBP	--	0.03
DBDPE	--	2.3
∑EFRs	--	47
BDE 47 [c]	19.3	16.3
BDE 100 [c]	2.7	2.2
BDE 99 [c]	4.2	4.0
BDE 154 [c]	1.7	1.3
BDE 153 [c]	6.5	5.3
Σtri-hexa BDEs [c]	34.9	29.4
BDE 209 [c]	1.8	1.2
α-HBCDD [d]	29	18
β-HBCDD [d]	1.8	1.8
γ-HBCDD [d]	4.2	3.3
∑HBCDDs [d]	35	22

a) Values below LOQ were assumed to be 1/2 LOQ; b) Based on an average body weight of 4.14 kg and a daily lipid intake of 24.4 g lipid/day (U.S. EPA, 2002); c) Data from Abdallah and Harrad (2014); d) Data from Abdallah and Harrad (2011).

Table S15: Estimated exposure [a, b] (ng/kg bw/day) of a 1 month old infant to target FRs via ingestion of breast milk sampled in 2014-15

	Mean	Median
α-DBE-DBCH	3.9	3.5
β-DBE-DBCH	15	7.1
EH-TBB	1.2	0.94
BTBPE	0.88	0.29
BEH-TEBP	1.5	0.03
DBDPE	--	2.3
∑EFRs	--	18
BDE 28	1.1	0.83
BDE 47	17	13
BDE 100	4.3	3.1
BDE 99	5.9	4.5
BDE 154	0.77	0.71
BDE 153	10	11
Σtri-hexa BDEs	38	34
BDE 209	0.65	0.65
α-HBCDD	12	11
β-HBCDD	1.5	1.4
γ-HBCDD	5.3	4.3
∑HBCDDs	19	17

a) based on levels in analysed human milk collected from 2014-2015 (n=10); values below LOQ were assumed to be 1/2 LOQ; b) Based on an average body weight of 4.14 kg and a daily lipid intake of 24.4 g lipid/day (U.S. EPA, 2002)

Table S16: Assumed absorption fractions and human half-lives of individual target FRs

EFR	molecular weight	number of bromines	PBDE	molecular weight	number of bromines	human half-lives of PBDE (days)	PBDE absorption fraction
DBE-DBCH	427.80	4	**BDE 47**	485.79	4	1096 [a]	0.58 [c]
EH-TBB	549.90	4	**BDE 47**	485.79	4	1096 [a]	0.58 [c]
BTBPE	687.60	6	**BDE 183**	722.48	7	94 [b]	0.90 [d]
BEH-TEBP	706.10	4	**BDE 183**	722.48	7	94 [b]	0.90 [d]
DBDPE	971.20	10	**BDE 209**	959.17	10	15 [b]	0.14 [c]

a) Geyer, H. J., Schramm, K.-W., Darnerud, P. O., Aune, M., Feicht, A., Fried, K. W., Mcdonald, T. a. (2004). Terminal elimination half-lives of the brominated flame retardants TBBPA , HBCD , and lower brominated PBDEs in humans. Organohalogen Compounds, 66, 3820–3825.; b) Thuresson, K., Höglund, P., Hagmar, L., Sjödin, A., Bergman, Å. ☒,& Jakobsson, K. (2006). Apparent half-lives of hepta- to decabrominated diphenyl ethers in human serum as determined in occupationally exposed workers. Environmental Health Perspectives, 114(2), 176–181.; c) Abdallah, M. A.-E., Tilston, E., Harrad, S., & Collins, C. (2012). In vitro assessment of the bioaccessibility of brominated flame retardants in indoor dust using a colon extended model of the human gastrointestinal tract. Journal of Environmental Monitoring, 14, 3276–3283.; d) Lorber, M. (2008). Exposure of Americans to polybrominated diphenyl ethers. Journal of Exposure Science and Environmental Epidemiology, 18(1), 2–19.

Table S17: Comparison of predicted adult body burdens arising from average and median daily exposures [a] to major target PBDEs with body burdens derived from observed concentrations in human milk sampled in 2014-15

	BDE 28	BDE 47	BDE 100	BDE 99	BDE 154	BDE 153	BDE 209
Average intake (ng/day) [b]							
Dust [c]	0.21	3.40	2.80	5.00	1.70	3.40	410
Diet [d]	2.50	45.54	11.40	54.98	7.07	5.11	6.20
Air [c]	0.40	2.20	0.51	1.50	0.09	0.16	4.20
Median intake (ng/day) [b]							
Dust [c]	0.01	0.50	0.11	0.82	0.05	0.49	100
Diet [d]	2.52	35.99	8.27	37.68	6.34	3.94	6.28
Air [c]	0.04	0.31	0.03	0.19	0.01	0.02	1.40
Average predicted body burdens (ng/g lw)							
Dust	0.03	0.18	0.13	0.18	0.09	0.58	0.07
Diet	0.41	2.39	0.53	1.93	0.39	0.87	0.001
Air	0.07	0.20	0.04	0.13	0.02	0.06	0.01
Sum	0.51	2.76	0.71	2.24	0.50	1.50	0.08
Median predicted body burdens (ng/g lw)							
Dust	0.002	0.03	0.01	0.03	0.003	0.08	0.02
Diet	0.41	1.89	0.39	1.32	0.35	0.67	0.001
Air	0.01	0.03	0.002	0.02	0.001	0.01	0.002
Sum	0.42	1.94	0.39	1.37	0.36	0.76	0.02
Observed body burdens (ng/g lw)							
Average	0.19	2.8	0.73	1.0	0.13	1.7	<0.22
Median	0.14	2.2	0.53	0.77	0.12	1.8	<0.22

a) Values below LOQ were assumed to be 1/2 LOQ; b) Based on average adult dust ingestion rate of 20 mg/day (Jones-Otazo et al., 2005) and average inhalation rate of 20 m^3/day (Currado and Harrad, 1998) and average adult weight of 70 kg; c) Data from Tao et al. (2016); d) Estimated from the average consumption rates calculated for each food group (Food Standards Agency, 2014), the average and median FRs concentrations in this study were used for calculation of average and median dietary intakes, separately.

Table S18: Comparison of predicted adult body burdens arising from average and median daily exposures [a] to HBCDDs with body burdens derived from observed levels in human milk sampled in 2014-15

	α-HBCDD	β-HBCDD	γ-HBCDD
Average intake (ng/day)			
Dust [e]	41.00	19.00	80.00
Diet [c,f]	16.77	5.40	7.43
Diet [d]	203.44	105.43	112.24
Air [e]	0.79	0.30	4.80
Median intake (ng/day)			
Dust [e]	9.20	2.70	3.00
Diet [c,f]	18.18	5.41	8.51
Diet [d]	203.44	105.43	112.24
Air [e]	0.03	0.02	2.00
Average predicted body burdens (ng/g lw)			
Dust	0.51	0.07	0.26
Diet [c]	0.21	0.02	0.02
Diet [d]	2.55	0.38	0.37
Air	0.01	0.001	0.02
Sum [c]	0.73	0.09	0.31
Sum [d]	3.07	0.45	0.65
Median predicted body burdens (ng/g lw)			
Dust	0.12	0.01	0.01
Diet [c]	0.34	0.03	0.05
Diet [d]	2.55	0.38	0.37
Air	0.0004	0.0001	0.01
Sum [c]	0.34	0.03	0.05
Sum [d]	2.66	0.39	0.39
Observed body burdens (ng/g lw)			
Average	2.10	0.25	0.90
Median	1.90	0.23	0.73

a) Values below LOQ were assumed to be 1/2 LOQ; b) Based on average adult dust ingestion rate of 20 mg/day (Jones-Otazo et al., 2005) and average inhalation rate of 20 m^3/day (Currado and Harrad, 1998) and average adult weight of 70 kg; c) Values based on food samples collected in 2015 in this study; d) Values based on food samples in a previous study (UK Food Standards Agency, 2006); e) Data from Tao et al. (2016); f) Estimated from the average consumption rates calculated for each food group (Food Standards Agency, 2014), the average and median FRs concentrations in this study were used for calculation of average and median dietary intakes, separately.

208 **Figure S1: Average concentrations of ∑PBDEs in food samples from this study compared with two UK previous studies (UK**
209 **Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009)**

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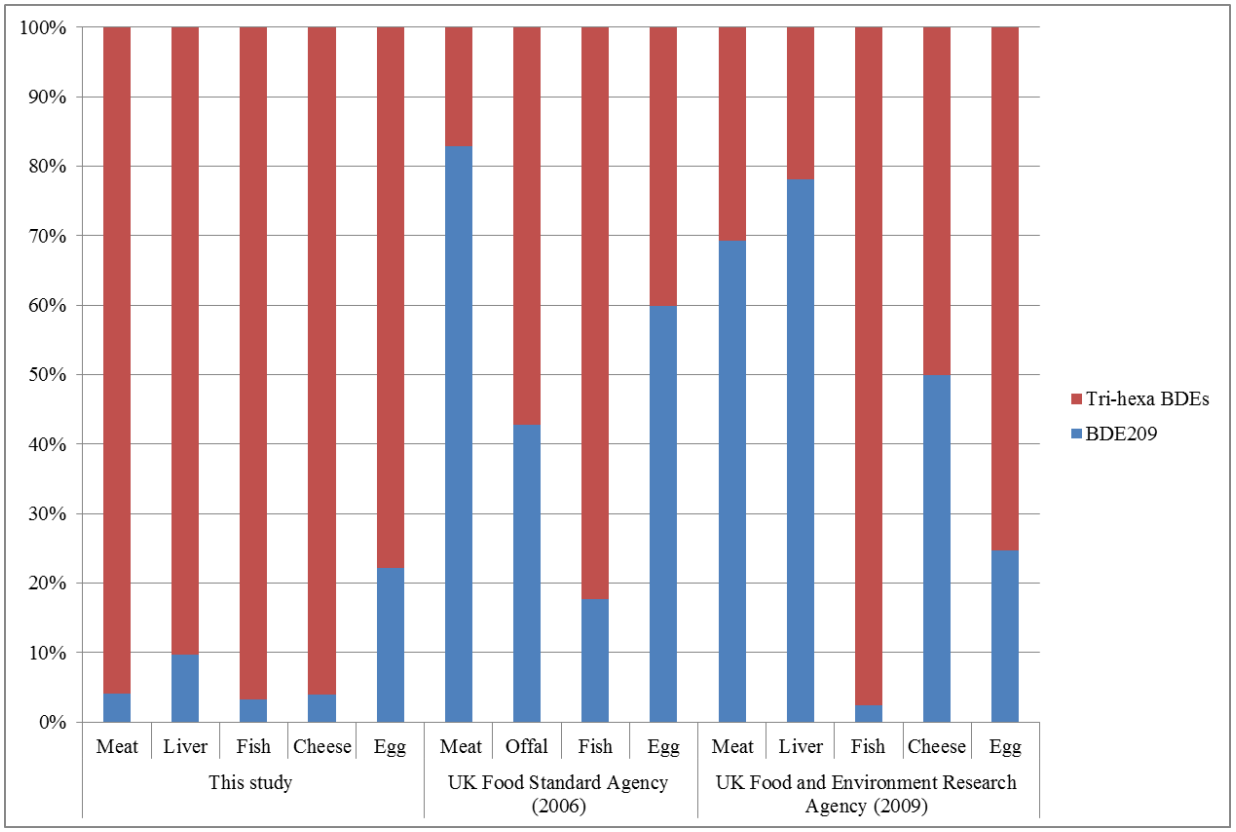
Figure S2: Relative contributions of tri-hexa-BDEs and BDE 209 to ∑PBDEs in UK food samples in this study and two previous studies



214 **Figure S3: Average concentrations of BDE209 in food samples from this study compared with two UK previous studies (UK**
215 **Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009)**

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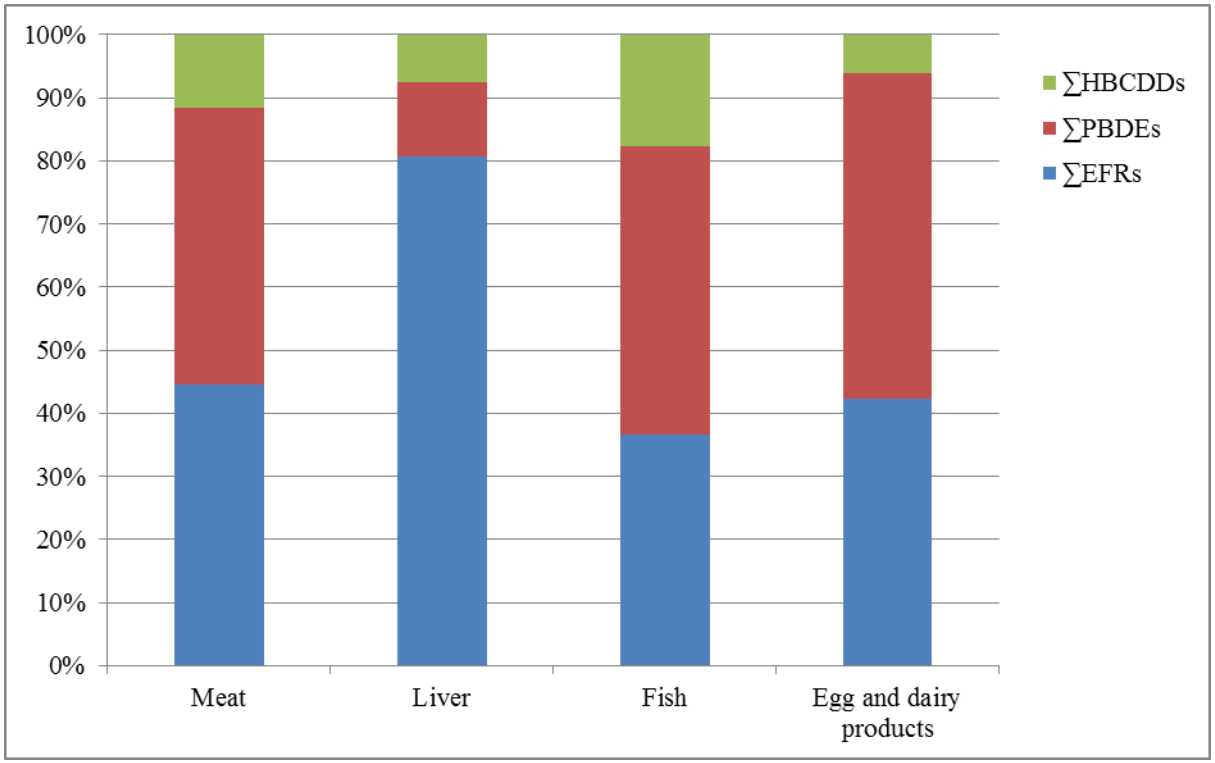
Figure S4: Average concentrations of Σtri-hexa BDEs in food samples from this study compared with two UK previous studies (UK Food Standards Agency, 2006; UK Food and Environment Research Agency, 2009)

223 **Figure S5: Relative contributions of EFRs, PBDEs and HBCDDs to ΣFRs in UK food samples**



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228 **Figure S6: Average relative contributions of EFRs, PBDEs and HBCDDs to ΣFRs in UK human milk**

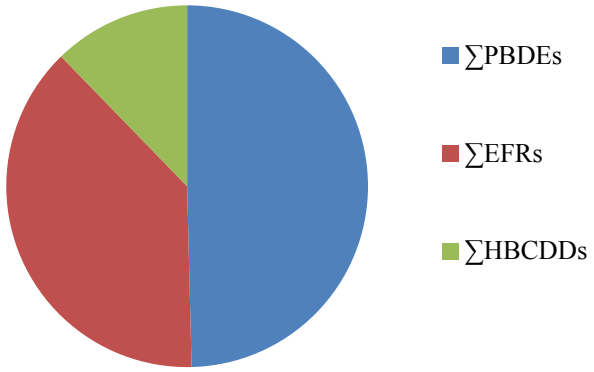

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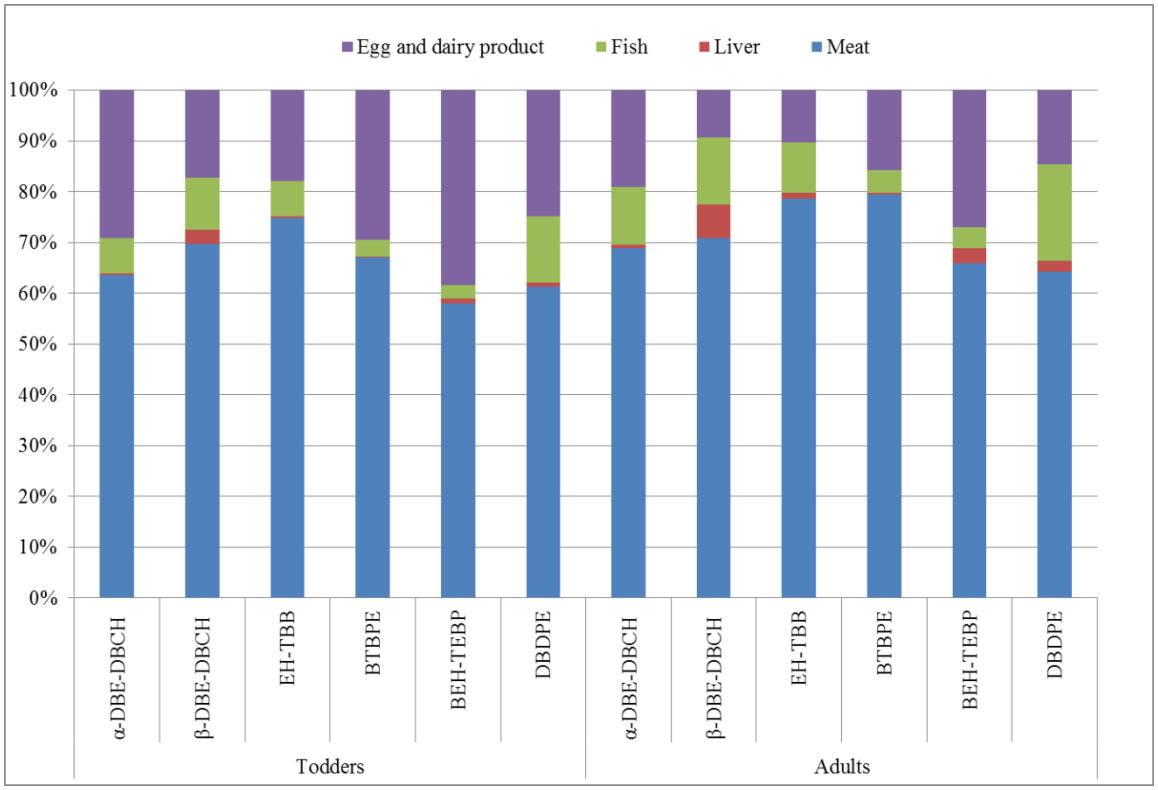
Figure S7: Contributions to average total dietary exposures for EFRs from different groups of UK food for toddlers and adults



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Highlights:

- First investigation of EFRs in UK human milk.
- Estimated dietary exposures to EFRs comparable to dietary intakes of PBDEs.
- β-DBE-DBCH most abundant EFR in food and human milk.
- No significant change in PBDEs and HBCDD in human milk between 2010 and 2014-15
- Nursing infant exposure to EFRs exceeds adult and toddler dietary intakes.
- Observed body burdens of EFRs match closely those predicted via PK modelling