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Emerging and legacy brominated flame retardants in the breast milk of first time Irish mothers suggest positive response to restrictions on use of HBCDD and Penta- and Octa-BDE formulations

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Abstract

The brominated flame retardants (BFRs) hexabromocyclododecane (HBCDD), eight polybrominated diphenyl ethers (PBDEs), and decabromodiphenyl ethane (DBDPE) were measured in 16 pools of human milk from Ireland. Concentrations of BDEs-47, -99, -100, -153, and HBCDD were significantly lower (p<0.05) than those in Irish human milk collected in 2011. In contrast, concentrations of BDE-209 in our study exceeded those in 2011, and while decabromodiphenyl ethane (DBDPE) was not detected in 2011 it was detected in 3 of our samples. This suggests increased use of DBDPE and that while restrictions on the Penta- and Octa-BDE formulations are reducing human exposure, those on Deca-BDE use have yet to reduce body burdens. Estimated exposures for nursing infants to all target BFRs do not suggest a health concern. A one compartment pharmacokinetic model was used to predict body burdens arising from BFR intakes via air, dust and diet. While for most targeted BFRs, predicted and observed body burdens derived from our human milk data compared reasonably well; predicted BDE-209 and DBDPE values were substantially lower than observed. This suggests exposure pathways not included in the model like dermal uptake from fabrics may be important, and highlights knowledge gaps about the human half-lives and bioavailability of these contaminants.

Keywords

Human biomonitoring, BFRs, DBDPE, temporal trends

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1. Introduction

Brominated flame retardants (BFRs) such as hexabromocyclododecane (HBCDD) and polybrominated diphenyl ethers (PBDEs) were until recently added to a range of consumer products worldwide to comply with fire safety standards. HBCDD was used in the manufacture of expanded and extruded polystyrene building insulation foams, as well as back-coatings of fabrics (Bromine Science and Environmental Forum (BSEF), 2003). The technical mixture contained primarily the γ-diastereomer but also the α- and β-diastereomers. Usage of PBDEs was in the guise of three commercial formulations: Penta-, Octa- and Deca-BDE. Penta- BDE was used principally in the manufacture of flexible polyurethane foams for soft furnishings, Octa-BDE in the manufacture of acrylonitrile butadiene styrene (ABS) used in housing for electrical and electronic equipment (EEE), while Deca-BDE was used in both high impact polystyrene (HIPS) housing for EEE and in fabrics (European Commission, 2011; UNEP, 2010; Weil and Levchik, 2009).

As a result of their widespread use, HBCDD and PBDEs are ubiquitous in the environment, and have been detected in a wide range of matrices, often in sites remote from where they were produced or used (Law et al., 2014). This, coupled with concerns regarding their toxicological profile, has led to their classification as persistent organic pollutants (POPs) under the Stockholm Convention (Secretariat of the Stockholm Convention, 2010), and legislative bans on their production and new use in various jurisdictions. Following these bans, replacement BFRs with similar chemical structures such as decabromodiphenyl ethane (DBDPE) have been marketed as “drop-in” replacements for the banned BFRs. Albemarle Corporation (Richmond, USA) introduced DBDPE in the early 1990s as a substitute to the commercial Deca-BDE mixture (Kierkegaard et al. 2004). Similar to PBDEs and HBCDD, DBDPE is an additive BFR and used in several polymeric materials, especially in electronic

equipment. China produced an estimated 12,000 tons in 2006 and an increase of 85% per year since (Hu et al 2008).

We recently reported elevated concentrations of DBDPE in Irish indoor air and dust that we hypothesized resulted from its use as a Deca-BDE replacement (Wemken et al., 2019). Moreover, we have previously reported evidence that suggested that in the UK – which has similar furniture flame retardancy regulations to those of Ireland (Alliance for Flame Retardant Free Furniture in Europe, 2017; Fire Safety Advice Center, 2011; Hagen et al., 2017; Irish Statute Book (eISB), 2015) - concentrations of PBDEs and HBCDD are falling in indoor dust, while those of "novel" BFRs like DBDPE have increased over the last decade (Tao et al., 2016). In contrast however, a related paper indicated that these changes had yet to be manifested in UK human milk (Tao et al., 2017). As concentrations of PBDEs, HBCDD, and DBDPE have been measured previously in 11 pooled samples of human milk collected from 109 Irish primiparas in 2011 (Pratt et al., 2013), we therefore wished to evaluate whether analysis of Irish human milk would reveal any significant responses to recent changes in the regulation and use of these BFRs. Consequently, this study reports concentrations of HBCDD, PBDEs, and DBDPE in 16 pooled samples of human breast milk collected from 92 Irish primiparas between October 2016 and April 2018.

We also wished to interpret our recently published data on Irish indoor exposures (Wemken et al., 2019) in conjunction with recent data on dietary exposure in the Republic of Ireland (Garcia Lopez et al., 2018), and evaluate the relative contributions of these different exposure pathways to human body burdens in Ireland. To do so, we apply here a simple one compartment pharmacokinetic model that predicts human body burdens of our target BFRs based on measured external exposures and knowledge of individual BFR human half-lives (Lorber, 2008; Tao et al., 2017). Comparison of these predicted body burdens with those

derived from our human milk measurements, provides insights into the accuracy of our external exposure estimates, and the human half-lives used as input to the model.

2. Materials and methods

2.1. Human milk sample Collection

With minor deviations, human milk sampling and donor recruitment adhered to the 4th WHO UNEP guidelines for developing a survey of human milk for persistent organic pollutants (WHO (World Health Organisation), 2007) and also those followed in a previous study that measured BFRs in Irish human milk (Pratt et al., 2013). Comparability of study design with this previous study was important to facilitate elucidation of temporal trends in BFR concentrations in human milk in Ireland. Study protocols and design were approved by the Clinical Research Ethics Committee of the Galway University Hospital (Ref: C.A. 1578) and the Research Ethics Committee of the Coombe Women & Infants University Hospital in Dublin (No. 30-2016).

Detailed sampling protocols are provided as Supporting Information (SI), but in summary breast milk samples were collected between 3 to 8 weeks postpartum from primiparas in good health and exclusively feeding one infant. Participants had to have resided at their current address for at least five years prior to sample collection. Although the WHO Guidance stipulates that participating mothers should be not older than 30 years; in Ireland, 65% of first time mothers are aged 30 – 40 years old (Central Statistics Office, 2018), and therefore recruitment selection criteria was amended to include mothers up to and including 40 years of age. This was in line with the previous Irish study which included mothers up to and including 41 years old (Pratt et al., 2013).

Mothers were recruited while attending breast feeding clinics at the same two Irish maternity hospitals from which mothers were recruited in a previous study, University Hospital Galway (UHG) (sampling period: October 2016- April 2018) and the Coombe Infant and Maternity Hospital (CIMH), Dublin (Sampling period: May 2017-April 2018). Breast milk samples of between 30 and 60 mL were collected from each participating mother in clean polypropylene bottles and stored at – 18 °C until further analysis.

A total of 92 breast milk samples were collected (UHG n=59; CIMH n=33). Samples were thawed and then pooled before analysis. Data provided by the mothers on the study questionnaire (see Supporting Information (SI)) were used to inform the creation of sixteen sample pools depending on their place of birth (Ireland, UK, EU, or non-EU), place of residence for the last five years (urban or rural) with two pools created that comprised samples from mothers indicating that they consumed fish at least twice a week (fish-consumer pools) (see SI, Table SI-4). Each pool contained aliquots of 30 mL of milk from each individual constituent sample (15 mL for the fish-consumer pools as there was less milk available from the individual donors to these pools), with the number of individual samples per pool ranging between 3 and 10. Following pooling, milk was freeze dried at -50 °C for 72 hours (using a Christ beta 1-8 LSC plus freeze drier) to prepare for analysis.

2.2. Sample preparation and analysis

Milk extraction and extract purification was conducted at the University of Birmingham in accordance with existing in-house protocols (Tao et al, 2017). Freeze dried breast milk (1 g) from each pool was loaded into a 66 mL stainless steel extraction cell, spiked with a known quantity of internal standard (BDE-77, BDE-128, $^{13}C_{12}$-BDE-209, $^{13}C_{12}$-α-HBCDD, $^{13}C_{12}$-β-HBCDD and $^{13}C_{12}$-γ-HBCDD) and extracted via Pressurized Liquid Extraction (ASE-350, Dionex, Sunnyvale, California, USA) using hexane and dichloromethane (3:1 v/v) at a temperature of 90 °C and a pressure of 1500 psi. Extractions consisted of three static cycles

with a static time of 5 minutes and the flush volume was 50 %. Crude extracts were concentrated to circa 0.5 mL using a Zymark Turbovap® II concentration workstation (Hopkinton, MA, USA), before being transferred to a 15 mL pyrex tube and vortexed for 1 minute with ca. 2 mL >95% concentrated sulfuric acid. The supernatant was then loaded on to an ENVI-Florisil SPE cartridge (500 mg/3 mL Sigma Aldrich) and target compounds eluted with 12 mL of 1:1 hexane/DCM. Samples were concentrated to near dryness and reconstituted in 50 µL toluene containing 0.1 ng/µL of PCB-129 and d_{18}-γ-HBCDD as recovery determination standards. Clean extracts were transferred to inserted autosampler vials ready for analysis (Abdallah et al., 2008).

2.3. Quality Assurance/Quality Control

A reagent blank was analysed with every batch of samples. None of the target compounds were detected in blank samples at concentrations exceeding 5 % of any of the sample concentrations. Therefore, results were not corrected for blank residues and method limits of quantification (LOQ) were estimated based on S/N = 10:1. Average LOQs ranged from 0.06 ng/g lipid to 0.3 ng/g for tri-through-octa-PBDEs, 0.6 ng/g for BDE-209, 2.5 ng/g lipid for DBDPE, and 0.05 ng/g lipid for individual HBCDDs (SI-Table 1).

2.4. Instrumental Analysis

DBDPE and PBDEs-28, 47, 99, 100, 153, 154, 183, and 209 were analyzed via GC-EI/MS using a Thermo Fisher Trace 1310 gas chromatograph coupled to a Thermo Fisher ISQ mass spectrometer using methods previously described (Wemken et al., 2019).

HBCDDs were analysed via LC-MS/MS using a Shimadzu LC-20AB Prominence binary pump liquid chromatograph, equipped with a SIL-20A autosampler, and a DGU-20A3 vacuum degasser, coupled to an AB Sciex API 2000 triple quadrupole MS. Full LC-MS/MS methods have been described previously (Abdallah et al., 2008).

2.5. Estimation of infant intake of FRs via breast milk

POPs can be transferred directly via breast milk to nursing infants. In order to evaluate a nursing infants' dietary intake of the target FRs in this study we used Equation (1):

$$Di = \frac{C_{BFR} x F_{lipid}}{BW} = ngkg^{-1} bw\ day^{-1} \text{ Eq (1)}$$

Where D_i is the estimated dietary intake (ng/kg bw/day); C_{BFR} is the median concentration of the given BFR in human milk (ng/g lw); F_{lipid} is the daily lipid intake via breast milk (g/day) and BW represents the child's body weight. To calculate F_{lipid}, U.S. EPA guidelines (USEPA, 2002) of average intake of 702 mL milk per day for a 1 month old infant weighing 4.14 kg were used. The median lipid content analysed was 3.47 g per 100 mL of breast milk resulting in a daily lipid intake of 24.4 g lipid per day.

2.6. First order Pharmacokinetic model for BFRs

A simple, one-compartment, first order pharmacokinetic (PK) model (Abdallah and Harrad, 2011) was used to investigate the relationship between predicted exposure intakes via various pathways and concentrations in human breastmilk. Target FRs were assumed to accumulate in lipids (single compartment in the model). Hence, the change in concentration in lipid of a given BFR over time can be calculated by Equation (2):

$$\frac{\delta C_{BFR}}{\delta t} = \frac{I_{BFR}(t) * AF_{BFR}}{BL_{(t)}} - K_{BFR} * C_{BFR}(t) \text{ Eq. (2)}$$

Where: C_{BFR} represents the BFR concentration normalised to milk lipid (ng/g lw); I_{BFR} stands for the daily intake of the BFR (ng/day); AF_{BFR} is the absorption fraction of the BFR; BL represents the body lipid mass (g) and K_{BFR} stands for the first order dissipation rate of the BFR (day^{-1}).

Eq. (2) can be changed thus, assuming constant K_{BFR} to yield Equation 3:

$$C_{FR}(t) = C_{FR}(0) * e^{(-K_{FR}*t)} + \left[\frac{I_{FR}(t)*AF_{FR}}{BL(t)}\right] * \left[\frac{(1-e^{(-K_{FR}*t)}}{K_{FR}}\right] \text{ Eq. (3)}$$

Where $C_{FR}(0)$ represents the target FR body lipid concentration at a time 0 (initial concentration before intake). Assuming a constant intake and body lipid mass (i.e. steady state), the steady state BFR lipid concentration can be calculated from Equation 4:

$$C_{BFR} = \frac{I_{BFR}(t)*AF_{BFR}}{BL(t)*K_{BFR}} \text{ Eq. (4)}$$

Note that the assumption of steady state conditions is an inherent uncertainty with this model.

Dust and diet absorption fractions and human half-lives for PBDEs and HBCDDs used in Eq. (4) were taken from the literature (Abdallah et al., 2012; Abdallah and Harrad, 2011; Geyer et al., 2004; Lorber, 2008; Thuresson et al., 2006) (Table SI-3). In the absence of experimental data to the contrary, inhaled BFRs were assumed 100% bioavailable. BL was calculated assuming an adult weighs 70 kg of which 25% is lipid (USEPA, 2002). K_{BFR} was determined as $0.693/t_{0.5}$; where $t_{0.5}$ is the half-life of the target BFRs in the body lipid compartment (Table SI-3).

Daily intakes for the Irish population via inhalation and dust ingestions were taken from measurements made in 2016-17 (Wemken et al., 2019), while estimated daily dietary intakes of PBDEs for the Irish population were obtained from the Food Safety Authority of Ireland (FSAI) based on foodstuffs collected in 2015 (Garcia Lopez et al., 2018; Tlustos et al., 2006;

Tlustos et al., 2005). As no Irish dietary data were available for DBDPE and HBCDD, UK dietary estimates were used (Tao et al, 2017; Food Standards Agency, 2006).

2.7. Statistical analysis

Statistical analysis was performed using Excel for Mac version 16.27. A t-test was used to compare concentrations in individual pools in the current study with those in individual pools reported in the 2011 study (Pratt et al., 2013) For the purposes of statistical analysis, for compounds where the detection frequency (DF) exceeded 50%, ½ LOQ was used for samples where the concentration of a given BFR was <LOQ. For compounds where the DF < 50%, the fractional detection frequency x LOQ was used.

3. Results & discussion

3.1. Concentrations and congener/isomer profiles of PBDEs and HBCDD in human breast milk from Ireland

A summary of concentrations and detection frequencies (DFs) for target BFRs in human milk samples measured in this study are presented in Table 1 (the full data set is presented in Table SI-3). Apart from BDE-28, 99, 100 and 154 (which were below their respective LOQs of 0.06, 0.2, 0.2 and 0.12 ng/g lw respectively in all pools), all target PBDE congeners and HBCDD diastereomers were detected in at least one sample pool, with BDE-47, 153 and α-HBCDD present in all. BDE-209 was detected in 81% of samples, and with respect to concentration was the dominant PBDE congener, accounting on average for 65% of $\Sigma PBDE_{28:209}$, followed by BDE-153 (18%) and BDE-47 (15%). This contrasts to the previous Irish survey of BFRs in human milk collected in 2011 (Pratt et al., 2013) (Table 1), where

although BDE-209 was still one of the most abundant congeners (21% $\Sigma PBDE_{28:209}$), it was less predominant than either BDE-47 (31% $\Sigma PBDE_{28:209}$) and BDE-153 (28% $\Sigma PBDE_{28:209}$). The concentrations of BDE-209 in our study (median 1.4 ng/g lw) are on the high end of those reported in European studies (Fromme et al., 2016). Specifically, they exceed those reported for UK human milk samples collected in both 2010 (median 0.25 ng/g lw) (Abdallah and Harrad, 2014) and between 2014 and 2015 (median <0.22 ng/g lw) (Tao et al., 2017), as well as those reported in samples collected in France and Finland between 2011 and 2014 (Antignac et al., 2016). The concentration of BDE-209 was noticeably elevated in pool 12 at 24 ng/g lw. The donor composition of this pool is not unusual in this study, comprising 7 urban and 1 rural dwellers from County Dublin (Table SI-4), nor are there any high fish eaters in this pool which may have provided a rationale for the elevated BDE-209 concentration. Instead, one possible explanation for the elevated BDE-209 in pool 12 is that some of the donors could have high exposures via dust ingestion. This is plausible, given our previous observations of BDE-209 concentrations in Irish house dust of up to 650,000 ng/g (Wemken et al., 2019).

$\Sigma PBDE_{28:183}$ concentrations in this study (average = 1.4 ng/g lw) are below those reported in the UK, Finland and Denmark (Abdallah and Harrad, 2014; Antignac et al., 2016) between 2010 and 2014, but exceed those reported in France for the same period (Antignac et al., 2016). BDE-153 followed by BDE-47 dominate our $\Sigma PBDE_{28:183}$ concentrations. A recent review revealed BDE-153 and -47 along with BDE-99 tend to dominate the $\Sigma PBDE_{28:183}$ profiles for human milk in most studies (Fromme et al., 2016). Moreover, over the last decade, the proportion of BDE-153 compared to BDE-47 has risen, with similar proportions of BDE-153 to those found in this study have been reported in Germany (52% of $\Sigma PBDE_{28:183}$) for studies performed in 2007 (Hoopmann et al., 2009). This increasing predominance of BDE-153 in human milk has been attributed to it possessing a longer human

half-life than other congeners, and to possible *in vivo* metabolism of higher molecular weight PBDEs to BDE-153 (Abdallah and Harrad, 2014).

Concentrations of ΣHBCDD (median 1.8 ng/g lw) in this study are slightly lower than those reported in samples collected in the UK in 2014-15 (2.9 ng/g lw; Tao et al., 2017) but exceed those reported in France, Denmark and Finland (Antignac et al., 2016) (for which only α-HBCDD was reported). The α-HBCDD diastereomer was dominant in our samples (on average 75% of ΣHBCDD). This is similar to previous studies of HBCDD in breast milk in which α-HBCDD typically contributes between 65–84% ΣHBCDD (Fromme et al., 2016).

3.2. Temporal trends in BFRs in Irish human milk

Using a t-test, we compared concentrations of individual PBDEs and ΣHBCDD in individual pools in our study with those reported for individual pools in the 2011 Irish study (Pratt et al., 2013). The detection limits in our study for BDEs -154 and -183 exceeded concentrations detected in all samples collected in 2011, resulting in only BDE-183 being detected in 1 sample in our study, and precluded meaningful statistical analysis of any temporal trend for these congeners. In contrast, concentrations of BDE-47, -99, -100, and -153 in samples from our study are significantly lower ($p<0.05$) compared to those recorded in samples taken in 2011 from mothers attending the same hospitals (Pratt et al., 2013). The decline in body burdens of these PBDEs is likely the impact of legislative bans on the use of the Penta- and Octa-BDE formulations, and is consistent with a recent report (Garcia Lopez et al., 2018) that concentrations of PBDEs in Irish foods collected in 2015 were lower than those collected in 2010 (Trudel et al., 2010). In addition, concentrations of ΣHBCDD in Irish human milk are significantly lower ($p<0.05$) in our study than in samples collected in 2011. This may also provide encouraging evidence that recent restrictions on the use of HBCDD in Ireland have had a beneficial impact on human body burdens. The evidence provided here of declines in

Irish human body burdens in concentrations of some PBDEs and HBCDD that contrasts with our recent findings for the UK (Tao et al., 2017) is welcome; and suggests that future studies in the UK and other locations where these BFRs have been restricted, will reveal similar declines in human body burdens. In contrast, and in line with our recent observations in the UK, BDE-209 concentrations in our study did not differ significantly from those reported previously (Pratt et al., 2013), suggesting no discernible response yet in Ireland to the restrictions on the manufacture and use of the Deca-BDE formulation, which took effect later than those on HBCDD, Penta-BDE, and Octa-BDE.

3.3. Concentrations and temporal trend of DBDPE in human breast milk from Ireland

There have been few reported studies of DBDPE concentrations in human milk and so limited comparisons can be made with our DBDPE data. Despite similar limits of detection in both studies (2.5 ng/g lw in this study and 2.1-2.5 ng/g lw in the Pratt et al., 2013 study), DBDPE was detected in three out of sixteen samples in this study, compared to none in Irish samples collected in 2010. This increasing detection rate is in line with an increase in detection frequency of DBDPE in UK human milk from 4% in samples collected in 2010 to 10% in those obtained in 2014-15 (Tao et al., 2017). This increased – albeit still low at 19% - detection frequency for DBDPE in Irish human milk in our study is likely related to our recent report of elevated concentrations of DBDPE in Irish indoor air and dust (Wemken et al., 2019). Concentrations of DBDPE measured in this study (range < 2.5 – 4.6 ng/g lw) compare with those reported in Canada for milk samples collected in 2008-09 (1.7-25 ng/g lw) (Zhou et al., 2014), in the UK in 2014-15 (range <0.78-58 ng/g lw) (Tao et al., 2017), in China in samples collected in 2011 (range 2.45-21.8 ng/g lw, Shi et al., 2016), and in New Zealand in 2008 (range 0.016-0.33 ng/g lw (Mannetje et al., 2013).

3.4. Nursing infants' dietary intake of FRs via breast milk

Table 2 summarizes estimated average and median intakes of our target BFRs via breast milk for a 1 month old infant assuming C_{BFR} (equation 1) are the average and median concentrations in breast milk in this study. Infant exposures to BDEs-47, -99, and -209 are all less than relevant USEPA reference dose values (USEPA, 2002). The estimate for BDE-209 (median 9.4 ng/kg bw/day) exceeds that based on UK human milk samples collected in 2014-15 (median 0.65 ng/kg bw/day; (Tao et al., 2017) and reported estimates for Germany and USA of 0.27 and 0.87 ng/kg bw/day respectively, calculated for 3 - 6 month old infants weighing 5 kg and consuming 30 mL of breast milk lipid per day (Fromme et al., 2016). Our exposure estimates for BDE-47 (median 2.6 ng/kg bw/day) accord with those for Germany (3.0 ng/kg bw/day), but are exceeded by those for the UK (13 ng/kg bw/day) and the USA (173 ng/kg bw/day) (Fromme et al., 2016; Tao et al., 2017). With respect to DBDPE, our exposure estimates (median 2.8 ng/kg bw/day) exceed slightly those reported for the UK (median 2.3 ng/kg bw/day; Tao et al., 2017) but are lower than estimates reported for China (Shi et al., 2016).

Exposure estimates in this study for ΣHBCDD (median 10 ng/kg bw/day) are slightly higher than those reported for Germany and the US (median 7.7 ng/kg bw/day and 6.6 ng/kg bw/day respectively; Fromme at al., 2016), but lower than that reported for the UK (median 17 ng/kg bw/day; Tao et al., 2017).

3.5. Relationship between BFR intakes and human body burdens

The relationship between external dietary, inhalation and ingestion exposure and human body burdens (indicated by concentrations in breast milk) was examined for PBDEs, HBCDD, and DBDPE, using a first order pharmacokinetic (PK) model (Table 3). Predicted body burdens were calculated using median and average exposure estimates for Ireland for air and dust

(Wemken et al., 2019) and dietary intake (FSAI, 2019). No estimates of dietary exposure to HBCDD or DBDPE are available for Ireland and thus UK data were used as a proxy for Irish dietary exposure (Tao et al., 2017; Food Standards Agency, 2006).

Predicted body burdens for BDE-47 and BDE-154 agree well with observed values recorded in our study, with dietary exposure the predominant exposure pathway. In contrast, our observed body burdens of BDE-153 exceed predicted values; this is most likely a result of the long half-life of BDE-153 (EFSA et al., 2011; Geyer et al., 2004), resulting in observed body burdens reflecting past as well as current exposure, as well via metabolic stepwise meta–meta debromination of BDE-209 *in vivo* to yield BDE-153 (Roberts et al., 2011). Discrepancies between predicted and measured exposures to BDE-209 whereby observed values exceed predicted exposures are more difficult to explain, given the short half-life of this congeners (Geyer et al., 2004). Possible reasons for the overestimation of the model are that the bioaccessibility and human half-life values used in the model for BDE-209 are underestimated (uncertainties regarding human half-lives of PBDEs have been noted by Wong et al, 2013), and that exposures such as dermal uptake from BDE-209-containing fabrics (Abdallah and Harrad, 2018) are not considered. While observed average DBDPE body burdens were <2.5 ng/g lw and thus hard to compare with predicted values; the fact that 3 samples in this study contained >3 ng DBDPE/g lw suggests that the PK model used here similarly underestimates body burdens of DBDPE. Additional uncertainty associated with our predicted DBDPE body burdens arises from the lack of Irish dietary exposure data for this BFR, with the result that we have used the UK dietary exposure estimate of Tao et al (2017).

Average and median predicted HBCDD body burdens exceed those observed in this study. This is likely a result of the dietary estimates used in the PK model, which in the absence of Irish dietary exposure data were based on UK estimates of dietary exposure (Food Standards Agency, 2006) that probably reflect higher dietary exposures in the past.

4. Conclusions

HBCDDs, PBDEs and DBDPE are present in Irish human milk, indicating ubiquitous exposure of the Irish population to these contaminants. Comparison with previously reported concentrations in Irish human milk samples collected in 2011 as part of a similarly-designed study, suggest decreasing body burdens of HBCDD and of BDEs-47, 99, 100, and 153 reflecting the positive impact of legislative restrictions and bans on the manufacture and use of HBCDD and the Penta-BDE and Octa-BDE formulations. While exposures of Irish nursing infants to the BFRs measured in this study do not exceed current health-based limit values of legislative standing and thus imply that such exposures are not of health concern; we note that other researchers have suggested much lower exposure limits – e.g. a maximal allowed intake level of 0.26 ng kg bw^{-1} d^{-1} for BDE-99 (de Winter-Sorkina et al, 2006). Moreover, in the USA use of the Penta-BDE formulation was substantially higher than elsewhere in the world (BSEF, 2003). As a consequence, we note a report that breast-fed infants in the USA ingesting human milk containing concentrations of BDEs-47 and -99 at or above the 90^{th} percentile level would exceed the RfD values for these PBDEs (Lyche et al, 2015). However, we also note that the USA human milk samples on which this observation were based date from 2002 before Penta-BDE was banned and when exposure levels were likely much higher than those currently. Notwithstanding these caveats, both the possibility of lower exposure limits in the future, and international differences in levels of exposure highlight the need for continued regular and frequent biomonitoring of human exposure to BFRs and related contaminants. In contrast to the decline in HBCDD and BDEs-47, 99, 100, and 153 - and consistent with our recent report of elevated concentrations of DBDPE in Irish indoor air and dust – DBDPE was detected in 19% of sample pools in our study compared to

none in 2011. Moreover, no significant decline was observed in concentrations of BDE-209, suggesting restrictions on the Deca-BDE formulation have yet to impact on Irish human body burdens, and that DBDPE exposure is rising. A one compartment PK model suggests that on average, dietary exposure may be the most prominent exposure pathway for our target BFRs, with the exception of BDE-209 and DBDPE, for which dust ingestion predominates. While there was reasonable agreement between predicted and observed body burdens for tri-octa-BDEs and HBCDD, predicted body burdens were markedly lower than observed for BDE-209 and DBDPE. This may be attributable to a combination of bioavailability and human half-lives being underestimated for these BFRs, and that exposure from pathways such as dermal uptake from BFR-treated fabrics are not considered in the model.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at…

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Emerging and legacy brominated flame retardants in the breast milk of first time Irish mothers suggest positive response to restrictions on use of HBCDD and Penta- and Octa-BDE formulations

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Abstract

The brominated flame retardants (BFRs) hexabromocyclododecane (HBCDD), eight polybrominated diphenyl ethers (PBDEs), and decabromodiphenyl ethane (DBDPE) were measured in 16 pools of human milk from Ireland. Concentrations of BDEs-47, -99, -100, -153, and HBCDD were significantly lower (p<0.05) than those in Irish human milk collected in 2011. In contrast, concentrations of BDE-209 in our study exceeded those in 2011, and while decabromodiphenyl ethane (DBDPE) was not detected in 2011 it was detected in 3 of our samples. This suggests increased use of DBDPE and that while restrictions on the Penta- and Octa-BDE formulations are reducing human exposure, those on Deca-BDE use have yet to reduce body burdens. Estimated exposures for nursing infants to all target BFRs do not suggest a health concern. A one compartment pharmacokinetic model was used to predict body burdens arising from BFR intakes via air, dust and diet. While for most targeted BFRs, predicted and observed body burdens derived from our human milk data compared reasonably well; predicted BDE-209 and DBDPE values were substantially lower than observed. This suggests exposure pathways not included in the model like dermal uptake from fabrics may be important, and highlights knowledge gaps about the human half-lives and bioavailability of these contaminants.

Keywords

Human biomonitoring, BFRs, DBDPE, temporal trends

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1. Introduction

Brominated flame retardants (BFRs) such as hexabromocyclododecane (HBCDD) and polybrominated diphenyl ethers (PBDEs) were until recently added to a range of consumer products worldwide to comply with fire safety standards. HBCDD was used in the manufacture of expanded and extruded polystyrene building insulation foams, as well as back-coatings of fabrics (Bromine Science and Environmental Forum (BSEF), 2003). The technical mixture contained primarily the γ-diastereomer but also the α- and β-diastereomers. Usage of PBDEs was in the guise of three commercial formulations: Penta-, Octa- and Deca-BDE. Penta- BDE was used principally in the manufacture of flexible polyurethane foams for soft furnishings, Octa-BDE in the manufacture of acrylonitrile butadiene styrene (ABS) used in housing for electrical and electronic equipment (EEE), while Deca-BDE was used in both high impact polystyrene (HIPS) housing for EEE and in fabrics (European Commission, 2011; UNEP, 2010; Weil and Levchik, 2009).

As a result of their widespread use, HBCDD and PBDEs are ubiquitous in the environment, and have been detected in a wide range of matrices, often in sites remote from where they were produced or used (Law et al., 2014). This, coupled with concerns regarding their toxicological profile, has led to their classification as persistent organic pollutants (POPs) under the Stockholm Convention (Secretariat of the Stockholm Convention, 2010), and legislative bans on their production and new use in various jurisdictions. Following these bans, replacement BFRs with similar chemical structures such as decabromodiphenyl ethane (DBDPE) have been marketed as “drop-in” replacements for the banned BFRs. Albemarle Corporation (Richmond, USA) introduced DBDPE in the early 1990s as a substitute to the commercial Deca-BDE mixture (Kierkegaard et al. 2004). Similar to PBDEs and HBCDD, DBDPE is an additive BFR and used in several polymeric materials, especially in electronic

equipment. China produced an estimated 12,000 tons in 2006 and an increase of 85% per year since (Hu et al 2008).

We recently reported elevated concentrations of DBDPE in Irish indoor air and dust that we hypothesized resulted from its use as a Deca-BDE replacement (Wemken et al., 2019). Moreover, we have previously reported evidence that suggested that in the UK – which has similar furniture flame retardancy regulations to those of Ireland (Alliance for Flame Retardant Free Furniture in Europe, 2017; Fire Safety Advice Center, 2011; Hagen et al., 2017; Irish Statute Book (eISB), 2015) - concentrations of PBDEs and HBCDD are falling in indoor dust, while those of "novel" BFRs like DBDPE have increased over the last decade (Tao et al., 2016). In contrast however, a related paper indicated that these changes had yet to be manifested in UK human milk (Tao et al., 2017). As concentrations of PBDEs, HBCDD, and DBDPE have been measured previously in 11 pooled samples of human milk collected from 109 Irish primiparas in 2011 (Pratt et al., 2013), we therefore wished to evaluate whether analysis of Irish human milk would reveal any significant responses to recent changes in the regulation and use of these BFRs. Consequently, this study reports concentrations of HBCDD, PBDEs, and DBDPE in 16 pooled samples of human breast milk collected from 92 Irish primiparas between October 2016 and April 2018.

We also wished to interpret our recently published data on Irish indoor exposures (Wemken et al., 2019) in conjunction with recent data on dietary exposure in the Republic of Ireland (Garcia Lopez et al., 2018), and evaluate the relative contributions of these different exposure pathways to human body burdens in Ireland. To do so, we apply here a simple one compartment pharmacokinetic model that predicts human body burdens of our target BFRs based on measured external exposures and knowledge of individual BFR human half-lives (Lorber, 2008; Tao et al., 2017). Comparison of these predicted body burdens with those

derived from our human milk measurements, provides insights into the accuracy of our external exposure estimates, and the human half-lives used as input to the model.

2. Materials and methods

2.1. Human milk sample Collection

With minor deviations, human milk sampling and donor recruitment adhered to the 4th WHO UNEP guidelines for developing a survey of human milk for persistent organic pollutants (WHO (World Health Organisation), 2007) and also those followed in a previous study that measured BFRs in Irish human milk (Pratt et al., 2013). Comparability of study design with this previous study was important to facilitate elucidation of temporal trends in BFR concentrations in human milk in Ireland. Study protocols and design were approved by the Clinical Research Ethics Committee of the Galway University Hospital (Ref: C.A. 1578) and the Research Ethics Committee of the Coombe Women & Infants University Hospital in Dublin (No. 30-2016).

Detailed sampling protocols are provided as Supporting Information (SI), but in summary breast milk samples were collected between 3 to 8 weeks postpartum from primiparas in good health and exclusively feeding one infant. Participants had to have resided at their current address for at least five years prior to sample collection. Although the WHO Guidance stipulates that participating mothers should be not older than 30 years; in Ireland, 65% of first time mothers are aged 30 – 40 years old (Central Statistics Office, 2018), and therefore recruitment selection criteria was amended to include mothers up to and including 40 years of age. This was in line with the previous Irish study which included mothers up to and including 41 years old (Pratt et al., 2013).

Mothers were recruited while attending breast feeding clinics at the same two Irish maternity hospitals from which mothers were recruited in a previous study, University Hospital Galway (UHG) (sampling period: October 2016- April 2018) and the Coombe Infant and Maternity Hospital (CIMH), Dublin (Sampling period: May 2017-April 2018). Breast milk samples of between 30 and 60 mL were collected from each participating mother in clean polypropylene bottles and stored at – 18 °C until further analysis.

A total of 92 breast milk samples were collected (UHG n=59; CIMH n=33). Samples were thawed and then pooled before analysis. Data provided by the mothers on the study questionnaire (see Supporting Information (SI)) were used to inform the creation of sixteen sample pools depending on their place of birth (Ireland, UK, EU, or non-EU), place of residence for the last five years (urban or rural) with two pools created that comprised samples from mothers indicating that they consumed fish at least twice a week (fish-consumer pools) (see SI, Table SI-4). Each pool contained aliquots of 30 mL of milk from each individual constituent sample (15 mL for the fish-consumer pools as there was less milk available from the individual donors to these pools), with the number of individual samples per pool ranging between 3 and 10. Following pooling, milk was freeze dried at -50 °C for 72 hours (using a Christ beta 1-8 LSC plus freeze drier) to prepare for analysis.

2.2. Sample preparation and analysis

Milk extraction and extract purification was conducted at the University of Birmingham in accordance with existing in-house protocols (Tao et al, 2017). Freeze dried breast milk (1 g) from each pool was loaded into a 66 mL stainless steel extraction cell, spiked with a known quantity of internal standard (BDE-77, BDE-128, $^{13}C_{12}$-BDE-209, $^{13}C_{12}$-α-HBCDD, $^{13}C_{12}$-β-HBCDD and $^{13}C_{12}$-γ-HBCDD) and extracted via Pressurized Liquid Extraction (ASE-350, Dionex, Sunnyvale, California, USA) using hexane and dichloromethane (3:1 v/v) at a temperature of 90 °C and a pressure of 1500 psi. Extractions consisted of three static cycles

with a static time of 5 minutes and the flush volume was 50 %. Crude extracts were concentrated to circa 0.5 mL using a Zymark Turbovap® II concentration workstation (Hopkinton, MA, USA), before being transferred to a 15 mL pyrex tube and vortexed for 1 minute with ca. 2 mL >95% concentrated sulfuric acid. The supernatant was then loaded on to an ENVI-Florisil SPE cartridge (500 mg/3 mL Sigma Aldrich) and target compounds eluted with 12 mL of 1:1 hexane/DCM. Samples were concentrated to near dryness and reconstituted in 50 µL toluene containing 0.1 ng/µL of PCB-129 and d_{18}-γ-HBCDD as recovery determination standards. Clean extracts were transferred to inserted autosampler vials ready for analysis (Abdallah et al., 2008).

2.3. Quality Assurance/Quality Control

A reagent blank was analysed with every batch of samples. None of the target compounds were detected in blank samples at concentrations exceeding 5 % of any of the sample concentrations. Therefore, results were not corrected for blank residues and method limits of quantification (LOQ) were estimated based on S/N = 10:1. Average LOQs ranged from 0.06 ng/g lipid to 0.3 ng/g for tri-through-octa-PBDEs, 0.6 ng/g for BDE-209, 2.5 ng/g lipid for DBDPE, and 0.05 ng/g lipid for individual HBCDDs (SI-Table 1).

2.4. Instrumental Analysis

DBDPE and PBDEs-28, 47, 99, 100, 153, 154, 183, and 209 were analyzed via GC-EI/MS using a Thermo Fisher Trace 1310 gas chromatograph coupled to a Thermo Fisher ISQ mass spectrometer using methods previously described (Wemken et al., 2019).

HBCDDs were analysed via LC-MS/MS using a Shimadzu LC-20AB Prominence binary pump liquid chromatograph, equipped with a SIL-20A autosampler, and a DGU-20A3 vacuum degasser, coupled to an AB Sciex API 2000 triple quadrupole MS. Full LC-MS/MS methods have been described previously (Abdallah et al., 2008).

2.5. Estimation of infant intake of FRs via breast milk

POPs can be transferred directly via breast milk to nursing infants. In order to evaluate a nursing infants' dietary intake of the target FRs in this study we used Equation (1):

$$Di = \frac{C_{BFR} x F_{lipid}}{BW} = ngkg^{-1} bw\ day^{-1} \text{ Eq (1)}$$

Where D_i is the estimated dietary intake (ng/kg bw/day); C_{BFR} is the median concentration of the given BFR in human milk (ng/g lw); F_{lipid} is the daily lipid intake via breast milk (g/day) and BW represents the child's body weight. To calculate F_{lipid}, U.S. EPA guidelines (USEPA, 2002) of average intake of 702 mL milk per day for a 1 month old infant weighing 4.14 kg were used. The median lipid content analysed was 3.47 g per 100 mL of breast milk resulting in a daily lipid intake of 24.4 g lipid per day.

2.6. First order Pharmacokinetic model for BFRs

A simple, one-compartment, first order pharmacokinetic (PK) model (Abdallah and Harrad, 2011) was used to investigate the relationship between predicted exposure intakes via various pathways and concentrations in human breastmilk. Target FRs were assumed to accumulate in lipids (single compartment in the model). Hence, the change in concentration in lipid of a given BFR over time can be calculated by Equation (2):

$$\frac{\delta C_{BFR}}{\delta t} = \frac{I_{BFR}(t) * AF_{BFR}}{BL_{(t)}} - K_{BFR} * C_{BFR}(t) \text{ Eq. (2)}$$

Where: C_{BFR} represents the BFR concentration normalised to milk lipid (ng/g lw); I_{BFR} stands for the daily intake of the BFR (ng/day); AF_{BFR} is the absorption fraction of the BFR; BL represents the body lipid mass (g) and K_{BFR} stands for the first order dissipation rate of the BFR (day^{-1}).

Eq. (2) can be changed thus, assuming constant K_{BFR} to yield Equation 3:

$$C_{FR}(t) = C_{FR}(0) * e^{(-K_{FR}*t)} + \left[\frac{I_{FR}(t)*AF_{FR}}{BL(t)}\right] * \left[\frac{(1-e^{(-K_{FR}*t)}}{K_{FR}}\right] \text{ Eq. (3)}$$

Where $C_{FR}(0)$ represents the target FR body lipid concentration at a time 0 (initial concentration before intake). Assuming a constant intake and body lipid mass (i.e. steady state), the steady state BFR lipid concentration can be calculated from Equation 4:

$$C_{BFR} = \frac{I_{BFR}(t)*AF_{BFR}}{BL(t)*K_{BFR}} \text{ Eq. (4)}$$

Note that the assumption of steady state conditions is an inherent uncertainty with this model.

Dust and diet absorption fractions and human half-lives for PBDEs and HBCDDs used in Eq. (4) were taken from the literature (Abdallah et al., 2012; Abdallah and Harrad, 2011; Geyer et al., 2004; Lorber, 2008; Thuresson et al., 2006) (Table SI-3). In the absence of experimental data to the contrary, inhaled BFRs were assumed 100% bioavailable. BL was calculated assuming an adult weighs 70 kg of which 25% is lipid (USEPA, 2002). K_{BFR} was determined as $0.693/t_{0.5}$; where $t_{0.5}$ is the half-life of the target BFRs in the body lipid compartment (Table SI-3).

Daily intakes for the Irish population via inhalation and dust ingestions were taken from measurements made in 2016-17 (Wemken et al., 2019), while estimated daily dietary intakes of PBDEs for the Irish population were obtained from the Food Safety Authority of Ireland (FSAI) based on foodstuffs collected in 2015 (Garcia Lopez et al., 2018; Tlustos et al., 2006;

Tlustos et al., 2005). As no Irish dietary data were available for DBDPE and HBCDD, UK dietary estimates were used (Tao et al, 2017; Food Standards Agency, 2006).

2.7. Statistical analysis

Statistical analysis was performed using Excel for Mac version 16.27. A t-test was used to compare concentrations in individual pools in the current study with those in individual pools reported in the 2011 study (Pratt et al., 2013) For the purposes of statistical analysis, for compounds where the detection frequency (DF) exceeded 50%, ½ LOQ was used for samples where the concentration of a given BFR was <LOQ. For compounds where the DF < 50%, the fractional detection frequency x LOQ was used.

3. Results & discussion

3.1. Concentrations and congener/isomer profiles of PBDEs and HBCDD in human breast milk from Ireland

A summary of concentrations and detection frequencies (DFs) for target BFRs in human milk samples measured in this study are presented in Table 1 (the full data set is presented in Table SI-3). Apart from BDE-28, 99, 100 and 154 (which were below their respective LOQs of 0.06, 0.2, 0.2 and 0.12 ng/g lw respectively in all pools), all target PBDE congeners and HBCDD diastereomers were detected in at least one sample pool, with BDE-47, 153 and α-HBCDD present in all. BDE-209 was detected in 81% of samples, and with respect to concentration was the dominant PBDE congener, accounting on average for 65% of $\Sigma PBDE_{28:209}$, followed by BDE-153 (18%) and BDE-47 (15%). This contrasts to the previous Irish survey of BFRs in human milk collected in 2011 (Pratt et al., 2013) (Table 1), where

although BDE-209 was still one of the most abundant congeners (21% $\Sigma PBDE_{28:209}$), it was less predominant than either BDE-47 (31% $\Sigma PBDE_{28:209}$) and BDE-153 (28% $\Sigma PBDE_{28:209}$). The concentrations of BDE-209 in our study (median 1.4 ng/g lw) are on the high end of those reported in European studies (Fromme et al., 2016). Specifically, they exceed those reported for UK human milk samples collected in both 2010 (median 0.25 ng/g lw) (Abdallah and Harrad, 2014) and between 2014 and 2015 (median <0.22 ng/g lw) (Tao et al., 2017), as well as those reported in samples collected in France and Finland between 2011 and 2014 (Antignac et al., 2016). The concentration of BDE-209 was noticeably elevated in pool 12 at 24 ng/g lw. The donor composition of this pool is not unusual in this study, comprising 7 urban and 1 rural dwellers from County Dublin (Table SI-4), nor are there any high fish eaters in this pool which may have provided a rationale for the elevated BDE-209 concentration. Instead, one possible explanation for the elevated BDE-209 in pool 12 is that some of the donors could have high exposures via dust ingestion. This is plausible, given our previous observations of BDE-209 concentrations in Irish house dust of up to 650,000 ng/g (Wemken et al., 2019).

$\Sigma PBDE_{28:183}$ concentrations in this study (average = 1.4 ng/g lw) are below those reported in the UK, Finland and Denmark (Abdallah and Harrad, 2014; Antignac et al., 2016) between 2010 and 2014, but exceed those reported in France for the same period (Antignac et al., 2016). BDE-153 followed by BDE-47 dominate our $\Sigma PBDE_{28:183}$ concentrations. A recent review revealed BDE-153 and -47 along with BDE-99 tend to dominate the $\Sigma PBDE_{28:183}$ profiles for human milk in most studies (Fromme et al., 2016). Moreover, over the last decade, the proportion of BDE-153 compared to BDE-47 has risen, with similar proportions of BDE-153 to those found in this study have been reported in Germany (52% of $\Sigma PBDE_{28:183}$) for studies performed in 2007 (Hoopmann et al., 2009). This increasing predominance of BDE-153 in human milk has been attributed to it possessing a longer human

half-life than other congeners, and to possible *in vivo* metabolism of higher molecular weight PBDEs to BDE-153 (Abdallah and Harrad, 2014).

Concentrations of ΣHBCDD (median 1.8 ng/g lw) in this study are slightly lower than those reported in samples collected in the UK in 2014-15 (2.9 ng/g lw; Tao et al., 2017) but exceed those reported in France, Denmark and Finland (Antignac et al., 2016) (for which only α-HBCDD was reported). The α-HBCDD diastereomer was dominant in our samples (on average 75% of ΣHBCDD). This is similar to previous studies of HBCDD in breast milk in which α-HBCDD typically contributes between 65–84% ΣHBCDD (Fromme et al., 2016).

3.2. Temporal trends in BFRs in Irish human milk

Using a t-test, we compared concentrations of individual PBDEs and ΣHBCDD in individual pools in our study with those reported for individual pools in the 2011 Irish study (Pratt et al., 2013). The detection limits in our study for BDEs -154 and -183 exceeded concentrations detected in all samples collected in 2011, resulting in only BDE-183 being detected in 1 sample in our study, and precluded meaningful statistical analysis of any temporal trend for these congeners. In contrast, concentrations of BDE-47, -99, -100, and -153 in samples from our study are significantly lower ($p<0.05$) compared to those recorded in samples taken in 2011 from mothers attending the same hospitals (Pratt et al., 2013). The decline in body burdens of these PBDEs is likely the impact of legislative bans on the use of the Penta- and Octa-BDE formulations, and is consistent with a recent report (Garcia Lopez et al., 2018) that concentrations of PBDEs in Irish foods collected in 2015 were lower than those collected in 2010 (Trudel et al., 2010). In addition, concentrations of ΣHBCDD in Irish human milk are significantly lower ($p<0.05$) in our study than in samples collected in 2011. This may also provide encouraging evidence that recent restrictions on the use of HBCDD in Ireland have had a beneficial impact on human body burdens. The evidence provided here of declines in

Irish human body burdens in concentrations of some PBDEs and HBCDD that contrasts with our recent findings for the UK (Tao et al., 2017) is welcome; and suggests that future studies in the UK and other locations where these BFRs have been restricted, will reveal similar declines in human body burdens. In contrast, and in line with our recent observations in the UK, BDE-209 concentrations in our study did not differ significantly from those reported previously (Pratt et al., 2013), suggesting no discernible response yet in Ireland to the restrictions on the manufacture and use of the Deca-BDE formulation, which took effect later than those on HBCDD, Penta-BDE, and Octa-BDE.

3.3. Concentrations and temporal trend of DBDPE in human breast milk from Ireland

There have been few reported studies of DBDPE concentrations in human milk and so limited comparisons can be made with our DBDPE data. Despite similar limits of detection in both studies (2.5 ng/g lw in this study and 2.1-2.5 ng/g lw in the Pratt et al., 2013 study), DBDPE was detected in three out of sixteen samples in this study, compared to none in Irish samples collected in 2010. This increasing detection rate is in line with an increase in detection frequency of DBDPE in UK human milk from 4% in samples collected in 2010 to 10% in those obtained in 2014-15 (Tao et al., 2017). This increased – albeit still low at 19% - detection frequency for DBDPE in Irish human milk in our study is likely related to our recent report of elevated concentrations of DBDPE in Irish indoor air and dust (Wemken et al., 2019). Concentrations of DBDPE measured in this study (range < 2.5 – 4.6 ng/g lw) compare with those reported in Canada for milk samples collected in 2008-09 (1.7-25 ng/g lw) (Zhou et al., 2014), in the UK in 2014-15 (range <0.78-58 ng/g lw) (Tao et al., 2017), in China in samples collected in 2011 (range 2.45-21.8 ng/g lw, Shi et al., 2016), and in New Zealand in 2008 (range 0.016-0.33 ng/g lw (Mannetje et al., 2013).

3.4. Nursing infants' dietary intake of FRs via breast milk

Table 2 summarizes estimated average and median intakes of our target BFRs via breast milk for a 1 month old infant assuming C_{BFR} (equation 1) are the average and median concentrations in breast milk in this study. Infant exposures to BDEs-47, -99, and -209 are all less than relevant USEPA reference dose values (USEPA, 2002). The estimate for BDE-209 (median 9.4 ng/kg bw/day) exceeds that based on UK human milk samples collected in 2014-15 (median 0.65 ng/kg bw/day; (Tao et al., 2017) and reported estimates for Germany and USA of 0.27 and 0.87 ng/kg bw/day respectively, calculated for 3 - 6 month old infants weighing 5 kg and consuming 30 mL of breast milk lipid per day (Fromme et al., 2016). Our exposure estimates for BDE-47 (median 2.6 ng/kg bw/day) accord with those for Germany (3.0 ng/kg bw/day), but are exceeded by those for the UK (13 ng/kg bw/day) and the USA (173 ng/kg bw/day) (Fromme et al., 2016; Tao et al., 2017). With respect to DBDPE, our exposure estimates (median 2.8 ng/kg bw/day) exceed slightly those reported for the UK (median 2.3 ng/kg bw/day; Tao et al., 2017) but are lower than estimates reported for China (Shi et al., 2016).

Exposure estimates in this study for ΣHBCDD (median 10 ng/kg bw/day) are slightly higher than those reported for Germany and the US (median 7.7 ng/kg bw/day and 6.6 ng/kg bw/day respectively; Fromme at al., 2016), but lower than that reported for the UK (median 17 ng/kg bw/day; Tao et al., 2017).

3.5. Relationship between BFR intakes and human body burdens

The relationship between external dietary, inhalation and ingestion exposure and human body burdens (indicated by concentrations in breast milk) was examined for PBDEs, HBCDD, and DBDPE, using a first order pharmacokinetic (PK) model (Table 3). Predicted body burdens were calculated using median and average exposure estimates for Ireland for air and dust

(Wemken et al., 2019) and dietary intake (FSAI, 2019). No estimates of dietary exposure to HBCDD or DBDPE are available for Ireland and thus UK data were used as a proxy for Irish dietary exposure (Tao et al., 2017; Food Standards Agency, 2006).

Predicted body burdens for BDE-47 and BDE-154 agree well with observed values recorded in our study, with dietary exposure the predominant exposure pathway. In contrast, our observed body burdens of BDE-153 exceed predicted values; this is most likely a result of the long half-life of BDE-153 (EFSA et al., 2011; Geyer et al., 2004), resulting in observed body burdens reflecting past as well as current exposure, as well via metabolic stepwise meta–meta debromination of BDE-209 *in vivo* to yield BDE-153 (Roberts et al., 2011). Discrepancies between predicted and measured exposures to BDE-209 whereby observed values exceed predicted exposures are more difficult to explain, given the short half-life of this congeners (Geyer et al., 2004). Possible reasons for the overestimation of the model are that the bioaccessibility and human half-life values used in the model for BDE-209 are underestimated (uncertainties regarding human half-lives of PBDEs have been noted by Wong et al, 2013), and that exposures such as dermal uptake from BDE-209-containing fabrics (Abdallah and Harrad, 2018) are not considered. While observed average DBDPE body burdens were <2.5 ng/g lw and thus hard to compare with predicted values; the fact that 3 samples in this study contained >3 ng DBDPE/g lw suggests that the PK model used here similarly underestimates body burdens of DBDPE. Additional uncertainty associated with our predicted DBDPE body burdens arises from the lack of Irish dietary exposure data for this BFR, with the result that we have used the UK dietary exposure estimate of Tao et al (2017).

Average and median predicted HBCDD body burdens exceed those observed in this study. This is likely a result of the dietary estimates used in the PK model, which in the absence of Irish dietary exposure data were based on UK estimates of dietary exposure (Food Standards Agency, 2006) that probably reflect higher dietary exposures in the past.

4. Conclusions

HBCDDs, PBDEs and DBDPE are present in Irish human milk, indicating ubiquitous exposure of the Irish population to these contaminants. Comparison with previously reported concentrations in Irish human milk samples collected in 2011 as part of a similarly-designed study, suggest decreasing body burdens of HBCDD and of BDEs-47, 99, 100, and 153 reflecting the positive impact of legislative restrictions and bans on the manufacture and use of HBCDD and the Penta-BDE and Octa-BDE formulations. While exposures of Irish nursing infants to the BFRs measured in this study do not exceed current health-based limit values of legislative standing and thus imply that such exposures are not of health concern; we note that other researchers have suggested much lower exposure limits – e.g. a maximal allowed intake level of 0.26 ng kg bw^{-1} d^{-1} for BDE-99 (de Winter-Sorkina et al, 2006). Moreover, in the USA use of the Penta-BDE formulation was substantially higher than elsewhere in the world (BSEF, 2003). As a consequence, we note a report that breast-fed infants in the USA ingesting human milk containing concentrations of BDEs-47 and -99 at or above the 90^{th} percentile level would exceed the RfD values for these PBDEs (Lyche et al, 2015). However, we also note that the USA human milk samples on which this observation were based date from 2002 before Penta-BDE was banned and when exposure levels were likely much higher than those currently. Notwithstanding these caveats, both the possibility of lower exposure limits in the future, and international differences in levels of exposure highlight the need for continued regular and frequent biomonitoring of human exposure to BFRs and related contaminants. In contrast to the decline in HBCDD and BDEs-47, 99, 100, and 153 - and consistent with our recent report of elevated concentrations of DBDPE in Irish indoor air and dust – DBDPE was detected in 19% of sample pools in our study compared to

none in 2011. Moreover, no significant decline was observed in concentrations of BDE-209, suggesting restrictions on the Deca-BDE formulation have yet to impact on Irish human body burdens, and that DBDPE exposure is rising. A one compartment PK model suggests that on average, dietary exposure may be the most prominent exposure pathway for our target BFRs, with the exception of BDE-209 and DBDPE, for which dust ingestion predominates. While there was reasonable agreement between predicted and observed body burdens for tri-octa-BDEs and HBCDD, predicted body burdens were markedly lower than observed for BDE-209 and DBDPE. This may be attributable to a combination of bioavailability and human half-lives being underestimated for these BFRs, and that exposure from pathways such as dermal uptake from BFR-treated fabrics are not considered in the model.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at…

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Table

Table 1: Descriptive statistics for PBDE, DBDPE and HBCDD concentrations (ng/g lipid weight) in 16 pooled human milk samples from Ireland and comparison with selected other studies

Country/ Reference	Statistical Parameter	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	$\sum PBDE_{28:183}$	BDE-209	$\sum PBDE_{28:209}$	DBDPE	α-HBCDD	β-HBCDD	γ-HBCDD	∑HBCDD
Ireland This study	Detection frequency (%)	0	100	0	0	100	0	6	na	81	na	19	100	88	81	na
	Average	<0.06	0.64	<0.2	<0.2	0.78	<0.12	<0.3	1.4	2.8	4.3	0.74	1.5	0.22	0.27	2
	Median	<0.06	0.50	<0.2	<0.2	0.71	<0.12	<0.3	1.4	1.4	2.5	<2.5	1.7	0.34	0.21	1.8
	Minimum	<0.06	0.16	<0.2	<0.2	0.44	<0.12	<0.3	0.61	<0.6	1.7	<2.5	0.66	<0.05	<0.05	0.83
	Maximum	<0.06	1.8	<0.2	<0.2	1.5	<0.12	0.4	2.5	23	24	4.6	3	0.53	1.5	3.6
Ireland (Pratt et al., 2013)	Median	0.09	1.1	0.27	0.31	1.0	0.02	0.03	2.8	0.77	3.6	<2.2-<2.5	2.6	0.3	0.4	2.9
UK (Abdallah and Harrad, 2014, 2011)	Median	Na	2.8	0.71	0.45	1.10	0.30	na	5.0	0.25	na	<0.78	4.91	0.32	0.73	3.83
UK (Tao et al., 2017)	Median	0.14	2.2	0.77	0.53	1.8	0.12	na	5.8	<0.22	na	<0.78	1.9	0.23	0.73	2.9
Denmark **Finland** **France** (Antignac et al., 2016)	Median	0.19 0.33 0.04	1.99 3.12 0.43	0.76 0.54 0.10	0.45 0.42 0.10	1.20 0.77 0.54	0.07 0.05 0.03	0.07 0.03 0.05	4.90 5.19 0.21	0.34 na 1.47	na na na	- - -	0.31 0.31 0.56	- - -	- - -	- - -
Germany (Hoopmann et al., 2009)	Median	Na	0.29	0.10	0.10	0.52	Na	na	na	na	-	-	-	-	-	-
Canada (Zhou et al., 2014)	Median	Na	na	na	Na	16	Na	na	na	na	na	<1.7	-	-	-	-
USA (Carignan et al., 2012)	Geometric Mean	-	-	-	-	-	-	-	-	-	-	-	0.71	0.08	0.20	1.02
USA (Wu et al., 2007)	Median	0.9	13.9	2.4	2.4	3.0	0.2	0.1	30.2	<DL	na	-	-	-	-	-
New Zealand (Mannetje et al., 2013)	Median	0.22	2.54	0.53	0.54	0.72	0.04	0.07	na	0.35	na	-	-	-	-	-
China	Median	-	-	-	-	-	-	-	-	-	8.06	-	-	-	-	-

(Shi et al., 2016)								

Na = not available

Table 2: Estimated exposure[ab] (ng/kg bw/day) of a 1 month old infant to target FRs via ingestion of breast milk contaminated at the average and median levels in this study to BFRs and DBDPE.

Congener/Diastereomer	Average	Median
BDE-28[c]	0.18	0.18
BDE-47	3.7	2.6
BDE-100[c]	0.59	0.59
BDE-99[c]	0.59	0.59
BDE-154[c]	0.35	0.35
BDE-153	4.6	4.4
BDE-183[c]	0.11	0.11
$\sum$PBDE $_{28:183}$	8.5	8.5
BDE-209	17	9.4
$\sum$PBDE $_{28:209}$	25	15
DBDPE[c]	2.8	2.8
α-HBCDD	8.8	7.7
β-HBCDD	1.3	1.1
γ-HBCDD	1.4	0.8
$\sum$HBCDD	12	10

[a] Values below LOQ were assumed to be ½ LOQ, where the DF was >50%, DF<50% the LOQ*DF;
[b] Based on a daily lipid intake of 24.4 lipid/day and an average body weight of 14.14 kg (U.S. EPA, 2002).
[c] Substantial uncertainty as DF<50%.

Table 3: Estimated average and median daily intakes[a] of selected target PBDEs, DBDPE and HBCDDs comparison of adult body burdens predicted using a simple pharmacokinetic model with those observed in human milk samples.

	BDE-47	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**BDE-183**	**Σ5BDEs**	**BDE-209**	**DBDPE**	**α-HBCD**	**β-HBCD**	**γ-HBCD**	**Σ HBCDs**
Average intake (ng/day)													
Dust[b]	0.45	0.79	0.14	0.060	0.065	0.11	1.5	880	610	5.2	2.0	5.9	9.5
Diet[c]	6.5	3.1	1.5	0.79	0.89	0.31	13	27	16	200	110	112	410
Air[b]	0.81	0.97	0.079	0.025	0.026	0.028	1.9	20	9.6	0.025	0.018	0.27	0.50
Median intake (ng/day)													
Dust[b]	0.16	0.25	0.0050	0.013	0.018	0.031	0.44	220	91	33	10	11	46
Diet[c]	3.8	2.7	0.64	0.68	0.49	0.26	8.5	24	9.5	200	110	110	410
Air[b]	0.073	0.16	0.024	0.023	0.024	0.028	0.33	9.4	1.1	0.60	0.28	2.6	3.4
Average predicted body burdens (ng/g lw)													
Dust	0.022	0.037	0.0050	0.0043	0.0042	0.0008	0.073	0.14	0.11	0.41	0.038	0.037	0.42
Diet	0.61	0.27	0.099	0.13	0.051	0.0021	1.2	0.0043	0.0027	2.5	0.38	0.37	3.8
Air	0.10	0.16	0.0080	0.0058	0.0052	0.0002	0.28	0.023	0.012	0.0082	0.0013	0.012	0.041
Sum	**0.74**	**0.46**	**0.11**	**0.14**	**0.060**	**0.0031**	**1.5**	**0.17**	**0.12**	**3.0**	**0.42**	**0.42**	**4.2**
Median predicted body burdens (ng/g lw)													
Dust	0.0077	0.012	0.0002	0.0009	0.0012	0.0002	0.022	0.035	0.016	0.066	0.0073	0.019	0.087
Diet	0.36	0.23	0.043	0.11	0.028	0.0018	0.77	0.0039	0.0017	2.5	0.38	0.37	3.8
Air	0.0092	0.025	0.0025	0.0054	0.0049	0.0002	0.047	0.011	0.0014	0.0003	0.0001	0.0012	0.0059
Sum	**0.37**	**0.27**	**0.046**	**0.12**	**0.034**	**0.0023**	**0.84**	**0.050**	**0.019**	**2.6**	**0.39**	**0.39**	**3.9**
Observed body burdens (ng/g lw)													
Average	0.64	<0.2	<0.2	0.78	<0.12	<0.3	1.4	2.8	<2.5	1.5	0.23	0.27	2.0
Median	0.50	<0.2	<0.2	0.71	<0.12	<0.3	1.4	1.4	<2.5	1.4	0.19	0.16	1.8

[a] Values below LOQ were assumed to be 1/2 LOQ; 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 for adults (Currado and Harrad, 1998).

[b] Data for Ireland from Wemken et al. (2019).

[c] Dietary exposures for PBDEs estimated from the average consumption rates calculated for each food group (Garcia Lopez et al., 2018; Tlustos et al., 2006; Tlustos et al., 2005), with upper bound (UB) values used. Those for DBDPE are taken from the UK (Tao et al, 2017), with those for HBCDDs also taken from UK data (Food Standards Agency, 2006).

Supplementary Material

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***conflict of Interest Statement**

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: