Concentrations of Polybrominated Diphenyl Ethers, Hexabromocyclododecanes and Tetrabromobisphenol-A in Breast Milk from United Kingdom Women Do Not Decrease over Twelve Months of Lactation

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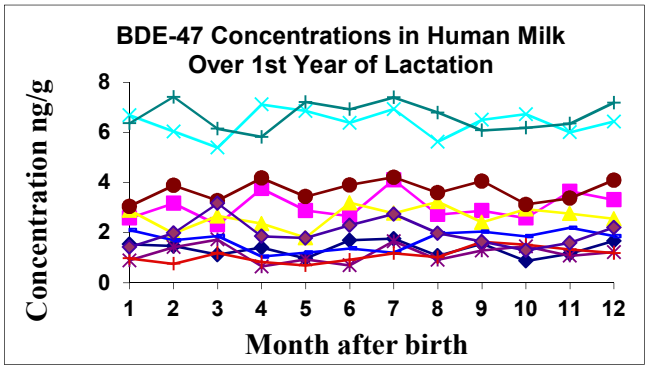

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Abstract

Conflicting evidence exists about whether concentrations of persistent organic chemicals in human milk decrease over the course of lactation. This has implications for the timing of sampling human milk for exposure assessment purposes. We examined this issue by measuring concentrations of polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDs), the HBCD degradation products tetrabromocyclododecenes (TBCDs), and tetrabromobisphenol-A (TBBP-A) in human milk collected in 2010-11 from 10 first-time mothers from Birmingham, UK. To evaluate whether concentrations varied significantly over the first 12 months post-partum, 12 samples were taken – one per month - from each mother, amounting to 120 samples overall. While concentrations of most of our target contaminants displayed no significant variation ($p>0.1$) over the duration of our study, significant increases were detected in concentrations of ΣTBCDs ($p=0.029$, average increase 1.4%/month) and BDE-153 ($p=0.058$, average increase 4.2%/month). When compared to data obtained from a different set of UK mothers from a related but geographically wider catchment area sampled contemporaneously to this study, the ratio of median concentrations of BDE-153 to BDE-99 was markedly lower in the current study (0.46 compared to 1.32). This may reflect unidentified differences in exposure of the participants in the two studies.

Introduction

Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and tetrabromobisphenol-A (TBBP-A) are chemicals that have found extensive global use as flame retardants incorporated within a wide range of goods and materials, such as electrical and electronic items, and soft furnishings. The extensive use of such brominated flame retardants (BFRs) has led to demonstrable contamination of both indoor and outdoor environments[1]. Contact with such contamination has led to human exposure via pathways such as inhalation of air, and ingestion of both food and indoor dust, and resulted in the ubiquitous presence of BFRs in humans[2, 3]. As with other persistent organic chemicals, concerns exist about the presence of BFRs in human milk. While studies to date of BFRs in human milk are consistent in demonstrating that breast-fed infants are exposed substantially via ingestion of human milk[4, 5]; conflicting findings have emerged from the small number of studies that have examined the temporal variation in concentrations of PBDEs in human milk from individual women over extended periods of lactation. Essentially, while some authors have reported no discernible consistent decrease of PBDE concentrations in human milk with increasing duration of lactation[6, 7]; others report PBDE concentrations in human milk over the first 6-18 months of lactation to decrease[8, 9]. Whether such temporal declines in PBDE contamination of human milk occur is of importance, as substantial reduction of concentrations over the course of lactation would mean analysis of milk samples taken soon after birth will both overestimate exposure of the nursing infant over the full period of lactation, as well as the reduction in mothers' body burdens as a consequence of lactation.

Given this background, we report here a study of human milk samples taken every month over the first year of lactation from 10 primiparas from Birmingham, UK. For each of these samples,

we report concentrations of PBDEs (including BDE-209), α–, β-, and γ-HBCDs, the HBCD degradation products tetrabromocyclododecenes (TBCDs), and TBBP-A. To our knowledge, these are the first data on temporal variation in concentrations in human milk from the same women, of TBCDs, and TBBP-A, as well as the first such data for individual HBCD diastereomers.

Methodology

Sample collection

Breast milk samples (each comprising ~50 mL) were obtained from 10 adult volunteers via Birmingham Women's Hospital Milk Bank, following approval of the study protocol by Warwickshire Research Ethics Committee and the R&D Department in Birmingham Women's NHS foundation trust. Informed consent was obtained from all participants before sample collection. Recruitment criteria were that mothers were healthy primiparas aged between 18 and 35, who were prepared to bring samples to the Milk Bank every month for the 12 month duration of the study. Samples collected in 2010-11 were kept in clean screw-capped glass containers and transferred from the Milk Bank to the laboratory in special ice boxes then stored at -20ºC until the time of analysis. Due to ethical regulations, the samples were collected in a completely anonymous fashion with all participant information kept strictly confidential. For the purposes of this study, a total of 12 milk samples were collected at monthly intervals from each mother commencing in the first month post-partum. All participants completed the study fully, with samples collected according to the same protocol by each participant throughout the course of the study.

Sample extraction

Samples were first freeze-dried, following the addition of 25 ng of each of ^{13}C-labeled BDE-47, BDE-99, BDE-153, BDE-209, TBBP-A, α–, β- and γ-HBCDs as internal (surrogate) standards. Accurately weighed aliquots of the freeze-dried samples (~ 2 g) were loaded into pre-cleaned 66 mL Accelerated Solvent Extraction (ASE 300, Dionex Inc., UK) cells containing 1.5 g florisil, 3 g alumina, 5 g anhydrous Na_2SO_4 and hydromatrix (Varian Inc., UK) to fill the void volume of the cells and spiked with 25 ng each of d_{18}-α-HBCD and ^{13}C-BDE-154 as QA/QC standards to evaluate losses due to extraction and clean-up. The ASE cells were extracted with hexane:dichloromethane (1:9, *v/v*) at 90 ˚C and 1500 psi. The heating time was 5 minutes, static time 4 min, purge time 90 s, flush volume 50%, with three static cycles. The lipid weight of the studied samples was determined gravimetrically on separate aliquots using a standard procedure (European Standard EN 1528-2, 1996; see supporting information for a summary).

Extract purification

The crude extracts were concentrated to 0.5 mL using a Zymark Turbovap® II (Hopkinton, MA, USA) then washed with 3 mL of 98 % sulfuric acid. After phase separation, the hexane layer was transferred onto a florisil column (1.5 g of 5% deactivated florisil, 60-100 mesh, topped with 1g of Sigma-Aldrich, UK)anhydrous sodium sulfate (Sigma-Aldrich, UK) and eluted with 25 mL of hexane:dichloromethane (1:1, v/v). The eluate was evaporated to dryness under a gentle stream of N_2 and the dried extract reconstituted in 200 μL of methanol containing 25 pg μL^{-1} of both $^{13}C_{12}$-BDE-100 and d_{18}-γ-HBCD used as recovery determination (or syringe) standards to determine recoveries of internal standards for QA/QC purposes.

LC-MS/MS analysis of PBDEs, HBCDs and TBBP-A

Concentrations of target BFRs were determined using an LC-MS/MS system composed of a dual pump Shimadzu LC-20AB Prominence liquid chromatograph equipped with SIL-20A autosampler, a DGU-20A3 vacuum degasser coupled to a Sciex API 2000 triple quadrupole mass spectrometer. The mass spectrometer was operated in atmospheric pressure photoionization mode (APPI) for the determination of PBDEs, and in electrospray ionization mode (ESI) to determine HBCDs, TBCDs, and TBBP-A. Full details of the multi-residue analytical methodology used for separation and quantification of our target compounds can be found elsewhere[4, 5, 10, 11].

Quality assurance/quality control

Full details of internal standard recoveries, field/method blanks, and method accuracy (measured by comparing our data with certified/indicative values for HBCDs and PBDEs for replicate analyses of NIST SRM2585, and matrix spikes at three concentration levels) have been reported previously[4,5]. A summary of these data is provided as supplementary information. Limits of quantification (LOQ) are also provided as SI. Where an analyte was <LOQ in a sample, it was substituted for the purposes of statistical analysis by f x LOQ – where f = fraction of samples in which the analyte was present >LOQ.

RESULTS AND DISCUSSION

Concentrations and patterns of BFRs in this study compared to other studies

Table 1 presents a statistical summary of concentrations of our target BFRs in this study, together with comparative data from selected other studies of BFRs in human milk. Table SI-1

gives concentrations of our target BFRs in every sample analyzed in this study. Concentrations of HBCDs and TBBP-A in this study fall within the range of those reported previously by our research group for single milk samples collected within the first 3 months post-partum from 35 women in the West Midlands conurbation[4]. This confirms that concentrations in UK mothers exceed ~5 fold those in Boston, USA[15], and are a little higher than those in Irish mothers[20]. Moreover, the HBCD diastereomer pattern is consistent with our previous study and most other studies worldwide. Specifically, α-HBCD was the predominant diastereomer observed contributing between 60 and 89% of ΣHBCDs, with an average of 79%. For comparison, α-HBCD contributed 62-95% ΣHBCDs in our earlier study[4]. With respect to TBBP-A, concentrations in this study are well below those of PBDEs and HBCDs – likely due to the short human half-life of TBBP-A[14] – and are consistent with the small number of previous reports of the presence of TBBP-A in human milk[4, 19, 20].

Our data also confirm previous reports of the presence of BDE-209 in human milk for which previous data are more limited than for other PBDEs, as well as providing only the second report of the presence of TBCDs in humans. As stated previously, the origins of TBCDs in humans are unclear; while they have been detected in indoor dust[12], they have also been shown to be formed as HBCD metabolites in *in vitro* experiments involving cultured human hepatocytes[13]. Of note, is the fact that median concentrations in this study of PBDEs 47, 153, and 209 are all lower than reported in our earlier study of single milk samples[5]. Furthermore, while in our earlier study, BDE-153 was more prevalent than BDE-99; the reverse was true in this study, and indeed median concentrations of BDE-99 are higher in the current study. As all QA/QC criteria in this study were met, and identical sampling, storage, and analytical protocols were followed in both studies, we do not believe these differences to result from measurement artefacts. Moreover, the

relative abundance of BDEs-99 and -153 in samples taken in this study during the first 3 months post-partum (samples in our earlier studies were collected during this period), was not discernibly different to those in later samples. Hence, the different timing of sample procurement in the two studies does not account for the different congener pattern. In addition, while the average age of participating mothers in the current study was 26.3 years, slightly lower than that of the mothers in the earlier study (28.3 years), the difference was not significant (t-test, $p>0.1$). Moreover, the mothers in both studies were all primiparas. Instead, we believe that the different congener pattern in the current study, reflects unidentified differences in exposure of the participants in the two studies. Pertinently, mothers in the current study did not participate in our earlier survey, and came from a more geographically restricted area close to the Birmingham Women's Hospital compared to participants in the earlier study who were recruited from across the West Midlands conurbation. Interestingly, based on data suggesting that BDEs-47 and -99 display shorter human half-lives than BDE-153[14]; Thomsen et al[18] identified an exposure scenario consistent with our observations. Specifically, they hypothesized that mothers with low background exposure due mainly to diet would be expected to be exposed to a higher proportion of BDE-153. Conversely, mothers receiving major direct exposure via contact with flame retarded products and indoor dust would display higher relative abundance of BDE-47 and BDE-99 in breast milk.

Comparison of our data with recent studies conducted in the US[7], New Zealand[16], and elsewhere in Europe[17-20] (Table 1) reveals mothers in this study to display concentrations of BDEs- 47, -99, and -153 that are in line with those from other regions, with the exception of the USA, in which concentrations of these congeners in humans are much higher than elsewhere in the world[7]. In contrast, as noted previously[5], the elevated concentrations of BDE-209 in UK indoor dust

compared to other countries[21] are not reflected in similarly elevated concentrations of this congener in human milk from UK mothers compared to women from other locations. While this may indicate poor bioavailability of BDE-209 from indoor dust[22], we note that BDE-209 concentrations in West Midlands mothers are lower than those detected in 6 mothers from north east England[17], and further data are required to ascertain whether the low BDE-209 concentrations in this study reflect a specific exposure pattern of our participants that is atypical of UK women in general.

Temporal variations in concentrations of BFRs in milk from individual mothers

To evaluate whether concentrations of individual BFRs exhibited significant variation over the full year of lactation for our 10 participants, we plotted concentrations of individual BFRs in each monthly sample as a percentage of the concentration detected in the first sample from the same mother. The plots obtained for BDE-47, BDE-153, ΣHBCDs, and ΣTBCDs are provided as Figure 1, with plots for other BFRs provided as supplementary information (Figure SI-1). With the exception of BDE-153 and ΣTBCDs, correlation analysis of these plots (conducted using Excel for Mac 2008) revealed there to be no significant change in concentration with time over the 12 months lactation covered by this study. In contrast, concentrations of both BDE-153 and ΣTBCDs show a significant increase (average increase 4.2% and 1.4%/month respectively) in concentrations during our study ($p=0.058$ and $p=0.029$ respectively).

A previous study reported concentrations of tri- through-deca-PBDEs in samples of human milk from 10 women in Oslo, Norway at monthly intervals on between 3 and 10 separate occasions per mother[9]. The authors reported that when normalized to concentrations in the first sample of each mother, concentrations of PBDEs 28, 47, 99, 100, 153, and 154 in subsequent samples

displayed a significant decrease over the period studied. These decreases ranged between 1.7%/month for BDE-153 and 4.7%/month for BDE-154. A similar study of primiparae women from California, reported PBDE concentrations in milk sampled every 4 weeks on 6 occasions from birth for 9 women, and in milk sampled on 2 occasions at varying time intervals between 18 and >85 weeks from birth for a further 9 women[8]. The authors of this study reported concentrations of BDE-47 to decline significantly by 3%/month on average, and 2%/month on average for both BDE-99 and BDE-100.

Clearly, our data contrast with these studies. However, they are consistent with the observations of two other studies[6, 7]. In the first of these, in which milk was sampled from 9 mothers on between 2 and 4 occasions up to nearly 1 year post-partum, concentrations of BDE-153 showed an increase in 7 mothers ($p=0.09$), but no clear, consistent decrease or increase was observed for any other targeted PBDEs[6]. In the second study, concentrations of PBDEs were measured in milk samples collected from 83 women at both 3 and 12 months post-partum[7]. As in the first study, while concentrations of BDE-153 were significantly higher in the 12 month samples ($p=0.005$), no significant change was observed for all other monitored PBDEs.

LaKind et al[6] offered two hypotheses to account for whether concentrations of POPs like PBDEs will change over the duration of lactation. The congener pattern observed in our study, whereby no significant temporal change was observed for most contaminants, but significant increases were seen for BDE-153 and ΣTBCDs; may conceivably be reconciled with the first of these hypotheses, that fluctuations in mothers' intake over the period monitored can influence concentrations in human milk. While little is known about human exposure to TBCDs, as highlighted above, Thomsen et al[18] identified that for PBDEs, a transition from exposure driven principally by indoor pathways such as direct contact with flame-retarded goods and indoor dust,

to background exposure driven mainly by diet, could result in an increase in the relative abundance of BDE-153 compared to BDEs 47 and 99. Given the hypothesized time-lag between reductions in PBDE exposure via the diet following reductions in indoor contamination[23] it is not inconceivable that our data is an indication of a response of the exposure of the UK population to PBDEs as a result of actions taken within the EU in the mid-2000s to restrict manufacture and use of the Penta- and Octa-BDE products.

The second hypothesis advanced by LaKind et al is that substantial post-partum weight loss can lead to increased (or at least less decreased) concentrations as a result of increased remobilization of contaminants associated with adipose tissue. Although due to the ethical constraints of our study, we do not have any information on the weight of our study participants, this does not at first seem a credible explanation for our data, given that concentrations increased for only two of our target contaminants. However, as these contaminants include BDE-153, for which recent human biomonitoring studies consistently indicate is constituting an increasing proportion of the ΣPBDE burden in human tissues[5, 18, 20], as a result of its greater persistence relative to other congeners[14, 24]; it is possible that our data reflect the impact of post-partum weight loss on BFR concentrations in our participants over a year of lactation. This could conceivably result in no overall temporal change for most BFRs, but an increase for BDE-153 given the temporal increase of this congener relative to other PBDEs reported elsewhere. If true, then this implies enhanced persistence in humans of ΣTBCDs relative to the parent HBCDs and the related PBCDs. In summary therefore, while we are unable to provide a definitive explanation for our observations; neither hypothesis outlined by LaKind et al can be ruled out.

This study – which has the highest temporal resolution of any conducted hitherto - provides substantial evidence that in a small group of UK mothers, concentrations in human milk of most

PBDEs, HBCDs, and TBBP-A do not change significantly over the first year of lactation. In contrast, concentrations of the more persistent BDE-153 congener, and the HBCD degradation product TBCDs display a significant increase over the same period. While a larger study involving more mothers is required to confirm our findings, our data suggest that for most of the major BFRs included in our study, human milk samples taken at any point in the first year post-partum will provide a reasonably representative measure of the exposure of the mother and the nursing infant. The reasons for the observed increase in concentrations of two BFRs are not clear, but may be related to *in vivo* metabolic production of these contaminants. In practical terms, the absence of any significant decline in BFR concentrations over the first year of lactation, suggests that advice to nursing mothers to practice pumping and discarding milk in the early stages of lactation (referred to colloquially as "pump and dump") in order to minimize infant exposure to such contaminants[8], is unlikely to be successful.

Acknowledgments

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Supplementary Information

Concentrations of all target contaminants in every sample analyzed; plots of concentrations of BDE-99, BDE-209, TBBP-A, α–, β–, and γ–HBCDs in each monthly sample as a percentage of the concentration detected in the first sample from the same mother; as well as detailed

descriptions of analytical methodology and QA/QC data. This information is available free of charge via the Internet at http://pubs.acs.org/.

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359 **Table 1: Summary of Concentrations (ng g^{-1} lipid weight) of Target BFRs in Human Milk in this Study and Others**

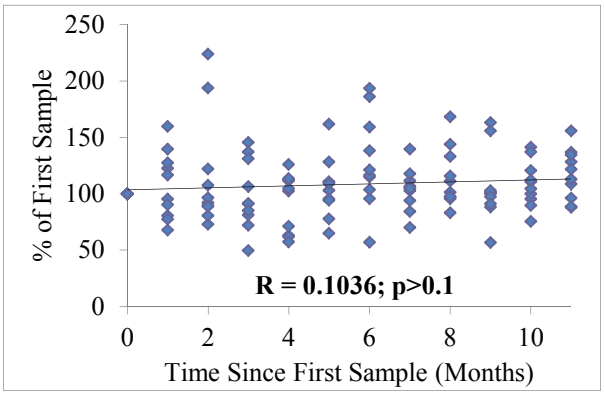
Location (n=number of participants)	Year of Sample Collection	Parameter	BDE-47	BDE-99	BDE-153	BDE-209	α-HBCD	β-HBCD	γ-HBCD	ΣTBCDs	TBBP-A
Birmingham, UK (n=10, 12 samples from each participant), this study	2010-11	5th %ile	0.89	0.38	0.07	0.05	1.64	0.09	0.12	0.01	0.03
		Median	2.30	1.04	0.48	0.08	4.16	0.40	0.76	0.11	0.04
		Average	2.97	1.58	0.51	0.14	5.27	0.48	0.79	0.14	0.06
		95th %ile	6.93	4.26	1.09	0.39	15.1	1.49	2.10	0.38	0.17
		DF* (%)	100	100	100	63	100	100	100	92	61
Birmingham, UK (n=35)[4]	2010	Median	NR	NR	NR	NR	3.17	0.30	0.56	0.14	<0.04
Birmingham, UK (n=34)[5]	2010	Median	2.80	0.69	0.91	0.25	NR	NR	NR	NR	NR
North East England, UK (n=6)[17]	2011-12	Median	2.05	0.97	0.93	0.70	NR	NR	NR	NR	NR
Boston, MA, USA (n=43)[15]	2005-06	Geometric Mean	NR	NR	NR	NR	0.71	0.08	0.20	0.05	<0.03NR0.55[a]
Central North Carolina, USA (n=303)[7]	2004-06	Median	28	5	6	NR**	NR	NR	NR	NR	NR
Norway (n=393)[18]	2001-2009	Median	0.99	0.27	0.45	0.32[b]	NR	NR	NR	NR	NR
France (n=23)[19]	2005	Median	NR	NR	0.83	1.50	NR	NR	NR	NR	0.17
Ireland (n=11[c])[20]	2010	Median	1.11	0.27	1.00	0.77[d]	2.59[e]	0.42[e]	0.43[e]	NR	0.05[e]
New Zealand (n=33)[16]	2010	Median	2.14	0.56	0.75	0.19	NR	NR	NR	NR	NR

360 [a] Range reported; geometric mean not reported due to low detection frequency for TBBP-A (35%)
361 [b] BDE-209 measured in a subset of 46 samples
362 [c] 11 pooled samples analyzed comprising milk from 109 primiparas
363 [d] BDE-209 analyzed in a subset of 10 pooled samples
364 [e] Lower bound average concentrations (i.e. where concentration below detection limit, concentration assumed to be zero)

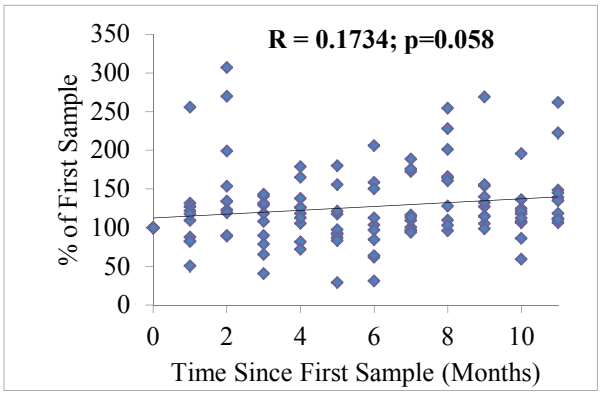
365 * DF refers to detection frequency; ** NR indicates the value was not reported.

Figure 1: Concentrations of BDE-47, BDE-153, ΣHBCDs, and ΣTBCDs normalized to the first sample

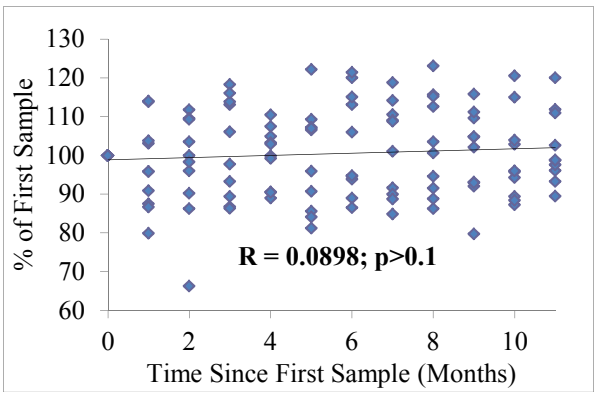
BDE-47



BDE-153



ΣHBCDs



ΣTBCDs