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SERUM MEASURES OF HEXABROMOCYCLODODECANE (HBCDD) AND POLYBORMINATED DIPHENYL ETHERS (PBDES) IN REPRODUCTIVE-AGED WOMEN IN THE UNITED KINGDOM

Daniel S Drage* [a,b], Amy L Heffernan,[b], Thomas K Cunningham[c], Lesa L Aylward[b,d], Jochen F Mueller[b], Thozhukat Sathyapalan[c], Stephen L Atkin[c,e]

[a] School of Geography, Earth and Environmental Sciences, University of Birmingham, Edgbaston, West Midlands, B15 2TT

[b]Queensland Alliance for Environmental Health Sciences, The University of Queensland, 39 Kessels Road, Coopers Plains, Qld 4108, Australia

[c]Academic Endocrinology, Diabetes and Metabolism, University of Hull/Hull and East Yorkshire Hospitals NHS Trust

Hull IVF Unit. The Women and Children's Hospital, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ

[d]Summit Toxicology, LLP, Falls Church, VA 22044 USA, USA

[e] Royal College of Surgeons Bahrain, Manama, Bahrain

*Corresponding Author

d.s.drage@bham.ac.uk

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Abstract

We investigated the serum concentrations of two brominated flame retardants (BFRs) – polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) –in 59 women aged between 23 and 42 from the United Kingdom. We also collected demographic data, including age, bodyweight and height in order to test for associations with BFR levels. Temporal and global differences were also assessed using previously published data.

HBCDD was detected in 68% of samples with a mean concentration of 2.2 ng/g lipid (range = <0.3 – 13 ng/g lipid). The dominant stereoisomer was α-HBCDD with an average contribution of 82% (0-100%) towards ΣHBCDD, was followed by γ-HBCDD (average contribution = 17%). PBDEs were detected in 95% of samples with a mean ∑PBDE (sum of BDEs -28, -47, -99, -100, -153, -154 and -183) concentration of 2.4 ng/g lipid (range = <0.4 – 15 ng/g lipid). BDEs -153 and -47 were the dominant congeners, contributing an average of 40% and 37% respectively, to the average ΣPBDE congener profile.

Data from this study suggests that HBCDD levels decrease with age, it also suggests a positive association between bodyweight and HBCDD levels, which likewise requires a large-scale study to confirm this. The data also show that 10 years after their European ban, PBDE body burden has begun to decrease in the UK. Whilst it is too early to draw any firm conclusions for HBCDDs, they appear to be following a similar pattern to PBDEs, with levels decreasing by a factor of >2.5 since 2010. Whilst the human body burden appear to be decreasing, both PBDEs and HBCDD are still consistently detected in human serum, despite legislative action limiting their production and use. This highlights the need to continuously assess human exposure and the effectiveness of policy aimed at reducing exposure.

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1.0 Introduction

Hexabromocyclododecane (HBCDD) and polybrominated diphenyl ethers (PBDEs) have been used extensively worldwide as brominated flame retardants (BFRs) in a wide variety of commercial, domestic and industrial applications. There are three commercial PBDE formulations – Penta-, Octa- and DecaBDE. The main PBDE applications include electrical and electronic equipment (EEE - such as TVs, PCs and small domestic appliances) (European Commission, 2011), soft furnishings (e.g. sofas, mattresses, pillows and curtains) (United Nations Environment Programme (UNEP), 2010) and in polyurethane foam (PUF) seat fillings used in automobiles (European Chemicals Bureau, 2000). The primary use of HBCDD is to flame retard expanded and extruded polystyrene (EPS/XPS) used in building insulation foam (European Chemicals Agency, 2009). As of 2001 (the last reliable figures publicly available), Europe accounted for 2 %, 16 %, 14 % and 57 % of the annual global demand for Penta-, Octa-, DecaBDE and HBCDD respectively (Bromine Science and Environmental Forum (BSEF), 2003).

Both PBDEs and HBCDD are lipophilic and resistant to metabolism allowing them to bioaccumulate in the liver and other fatty tissues. They have long half-lives in humans of approximately 664 – 2380 days and 64 days for PBDEs and HBCDD, respectively (Geyer et al., 2004), and have been associated with adverse health effects in humans.. For example, PBDEs are thought to disrupt levels of sex hormones, including luteinising hormone and follicle stimulating hormone in men (Meeker et al., 2009), in addition to other toxic effects including disruption to the liver, kidneys and thyroid gland; neurodevelopmental deficits including inhibited foetal and infant development; and various cancers (Costa, 2008). Furthermore, *in vitro* studies have demonstrated that doses as low as 5µM can induce oxidative stress and disrupt steroidogenesis, with high level PBDE exposure resulting in pregnancy

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failure (Lefevre et al., 2016). Exposure to the Penta-BDE formulation can activate the aryl hydrocarbon (Ah) –receptor (Gu et al., 2012), cause a reduction in hepatic vitamin A levels, impair neurodevelopment, and induce carcinogenesis (D'Silva et al., 2004, Hornung et al., 1996). Similarly, the OctaBDE formulation causes developmental toxicity, whilst the DecaBDE formulation is believed to be the least toxic as it contains higher molecular weight congeners that have relatively decreased cell membrane permeability, and are more readily metabolised (D'Silva et al., 2004, Chevrier et al., 2013). However, it is also believed that higher brominated congeners (such as BDE-209, which makes up >95% of the Deca-BDE formulation (La Guardia et al., 2006)) can be broken down by physical and biological processes to form lower brominated PBDE congeners that are found readily in Penta- and Octa-BDE formulations (D'Silva et al., 2004). Data on human health effects of HBCDD exposure is limited - Eggesbø et al., 2011 reported that it does not appear to have an effect on the human thyroid (Eggesbø et al., 2011). However, Dorosh et al. (2011) suggested its potential endocrine disrupting ability by altering oestrogenic activity.. Further, Genskow et al. (2015) has suggested that HBCDD exposure damages dopaminergic neurons, with consequences for neurological and endocrine system function, and there is evidence for reduced birthweight and significant adverse neurodevelopment, including impaired motor skills and increased anxiety levels in rodent models (Maurice et al., 2015).

Concerns over the toxicity of these BFRs led to bans on Penta- and Octa-BDE technical products within Europe in 2003, and globally in 2009 under the UNEP Stockholm Convention (SC) (Stockholm Convention, 2009). Significant restrictions were placed on the DecaBDE technical product in 2008 (Deffree, 2008), and it was included in the SC in 2017 (Chemical Watch, 2017), alongside HBCDD in 2013 (Health and Environment Alliance, 2013). Whilst these bans will eventually lead to reduced exposure, they only prevent the new manufacture

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and new use of these chemicals, meaning that BFRs will still be incorporated into products already on the market, and currently in circulation. Both PBDEs and HBCDDs are still regularly found in various indoor microenvironments across the world (Sahlstrom et al., 2015, Johnson et al., 2013, Ni and Zeng, 2013, Harrad and Abdallah, 2015), meaning that humans will continue to be exposed to them for the foreseeable future. Given that exposure to these chemicals can lead to a plethora of toxic health effects, it is vital that they are continually monitored in general populations across the globe.

The aims of this study are to provide the first data on HBCDD exposure in the UK population using human sera, and to provide updated assessment of human exposure to PBDEs and HBCDDs in reproductive-aged women in the UK. The relationship between these BFRs and various demographics (weight, body mass index (BMI), and age) will also be assessed to gain insight into any potential health effects caused by target compounds. We include a temporal assessment of HBCDD and PBDE body burdens in the UK, and a comparison of UK body burdens with available data from other cross-sectional populations, globally.

2.0 Materials & Methods

2.1 Sample Collection and Preparation

This prospective cohort study was performed within the Hull IVF Unit, UK in 2014, following approval by The Yorkshire and The Humber NRES ethical committee, UK (approval number 02/03/043). A total of 59 women were recruited into the study, whose baseline characteristics are shown in Table 1. Inclusion criteria were age 20-45 years, BMI ≤35 and undergoing *in vitro* fertilisation. Patients with known immunological disease, diabetes, renal or liver insufficiency, acute or chronic infections, or inflammatory diseases were excluded from the study.

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A fasting blood sample was collected on day 21 of the luteal phase of the cycle, and prior to commencing IVF treatment. Samples were centrifuged, aliquoted, and stored at -80 °C. Samples were shipped on dry ice to The Queensland Alliance for Environmental Health Sciences at The University of Queensland, Australia for further analysis.

2.2 Lipid Analyses of Samples

Serum (300µL) was analysed for cholesterol (TC) and triglycerides (TG) by Sullivan Nicolaides Pathology (SNP), Australia. Total lipid (TL) concentration (mg/dL) was calculated using the following equation (Phillips et al., 1989).

$$TL = 2.27.TC + TG + 62.3$$

2.3 Sample Extraction & Clean-up

Five mL of serum was aliquoted into a 50 mL polypropylene centrifuge tube. Samples were spiked with 5 ng each of internal standards ($^{13}C_{12}$-labelled BDEs -28, -47, -99, -100, -153, -154, -183, $^{13}C_{12}$-labelled α-, β- and γ-HBCDD). Samples were vortexed for approximately 1 minute and left to stand for 30 minutes. 6 mL acetonitrile, 3 mL milliQ, 5 g anhydrous $MgSO_4$ and 1 g NaCl were added along with a ceramic homogenizer. Samples were manually shaken for 1 minute prior to centrifuging at 4500 RPM for 8 minutes at 10 °C. The supernatant layer was collected and transferred to a glass tube. The extract was evaporated to near-dryness on a hot plate using a gentle stream of nitrogen and reconstituted in approximately 1 mL hexane. 1 mL >98% concentrated sulfuric acid was added and the sample was vortexed for at least 30 seconds. The aqueous and organic layers were left to separate overnight at <4 °C. The supernatant layer was transferred directly onto a silica solid phase extraction cartridge (Supelco LC-Si 3mL/500 mg), preconditioned with 6 mL dichloromethane, followed by 6 mL hexane. The sample was allowed to load onto the cartridge gravimetrically. Target compounds were

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eluted into a glass tube using 6 mL hexane, followed by 8 mL dichloromethane at approximately 2 mL/min. The sample was evaporated to near-dryness and reconstituted in 100 µL iso-octane containing 2.5 ng $^{13}C_{12}$-PCB-141 and $^{13}C_{12}$-TBBPA as recovery standards. After analysis for PBDEs by high resolution gas chromatography coupled with high resolution mass spectrometry (HRGC/HRMS) extracts were solvent exchanged into 100 µL methanol and analysed for HBCDD via liquid chromatography tandem mass spectrometry (LC-MS/MS).

2.4 Instrumental Analysis

For PBDE analysis by HRGC/HRMS,a Thermofisher TRACE 1300 gas chomatograph was coupled to a Thermofisher DFS mass spectrometer. The injector was operated in splitless mode with separation achieved on an Agilent DB-5ms column (30 m length x 0.25 mm in diameter x 0.25 µm film thickness). Experiments were conducted in MID mode at 10,000 resolution (10% valley definition). The inlet, transfer line and source were held at 250 ºC, 280 ºC and 280 ºC respectively. The flow rate was maintained at 1.0 mL/min. Details of acquisition ions for PBDEs are outlined in the supporting information (SI, (Tables S1 and S2 respectively).

HBCDDs (α-, β- and γ-) were measured in serum samples using an AB/Sciex API 5500Q mass spectrometer (AB/Sciex, Concord, Ontario, Canada) coupled to a Shimadzu Nexera HPLC system (Shimadzu Corp., Kyoto, Japan). The mass spectrometer (MS) was operated in multiple reaction monitoring mode using negative electrospray ionisation. A volume of 5 µL was injected. Separation was achieved using a Kinetex XB C18, 50 x 2.0 mm 1.7 µm column (Phenomenex, Torrance CA) using a mobile phase gradient of 85% methanol, ramping up to 100% methanol over 6 min and then holding for 4 min at a flow rate of 0.3 mL/min. Full MS parameters have been provided previously (Drage et al., 2017).

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171 *2.5 Quality Control*

172 A blank sample was extracted as every 6th sample (n=10), alternating between 5 mL of MilliQ
173 water (n=5) and 5 mL bovine calf serum (n=5). If a target compound was detected in a blank
174 at less than 5% of measured sample concentration, then no correction occurred; if blank
175 concentration was 5–25% of measured sample concentration, the blank concentration was
176 subtracted from that of the sample.

177

178 In the absence of a certified QC sample, method precision and accuracy were determined using
179 bovine serum (5mL, n=5) fortified with target compounds. 30 µL of a solution containing 2
180 ng/mL of all target compounds in methanol was added to each aliquot, which was then vortexed
181 for 1 minute and left at <4 °C overnight. Good accuracy and precision was found for all target
182 analytes with average recoveries between 80-120% and a relative standard deviation <15%
183 (Table S2).

184

185 Internal standard recoveries of ^{13}C-labelled HBCDDs were estimated by expressing their ratio
186 with $^{13}C_{12}$-TBBPA in the samples as a percentage of the same ratio in a non-extracted side-
187 spike (NESS). The recoveries of the remaining internal standards was calculated using their
188 ratio with $^{13}C_{12}$-PCB-141. Average recoveries ranged from 59% ($^{13}C_{12}$-BDE-28) to 84 %
189 ($^{13}C_{12}$-BDE-154). Details of recoveries of all internal standards are provided in the SI (Table
190 S3).

191

192 *2.6 Statistical Analysis*

193 For the purposes of calculations of averages and all statistical testing where a compound was
194 below the limit of quantification (LOQ), values were set to half the limit of detection (LOD).

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All statistical tests were computed using Microsoft Excel 2010 and SPSS for Windows version 22.0.

3.0 Results & Discussion

This study reports the first data for HBCDD in human serum from the UK. Sum of α-, β-, and γ-HBCDD (ΣHBCDD) was detected in 40 out of 59 samples at a concentration range of <0.3 – 13 ng/g lipid. The average concentration measured was 2.2 ng/g lipid, the geometric mean was 0.75 ng/g lipid and the median was 1.8 ng/g lipid (Table 2).

The dominant stereoisomer was α-HBCDD with an average contribution of 82% (0-100%) towards ΣHBCDD, was followed by γ-HBCDD (average contribution = 17%). β-HBCDD was only detected in one sample where it contributed 25% to a ΣHBCDD concentration of 11 ng/g lipid. This stereoisomer pattern in human sera is consistent with previous studies from Australia (Drage et al., 2017), India (Devanathan et al., 2012), Sweden (Weiss et al., 2006), Canada (Ryan et al., 2006) and Japan (Kakimoto et al., 2008). The dominance of α-HBCDD in human and other biotic samples is likely due to more effective transformation of β- and γ- HBCDD to α-HBCDD through increased metabolic rate, combined with preferential accumulation of the α-stereoisomer (Fonnum and Mariussen, 2009).

PBDEs were detected in measurable concentrations in 56 out of 59 samples with a ΣPBDE (sum of BDEs -28, 47, -99, -100, -153, -154 and -183) concentration range of <0.4 – 15 ng/g lipid. The average concentration was 2.4 ng/g lipid, the geometric mean was 1.4 ng/g lipid and the median was 1.9 ng/g lipid (Table 3). BDEs -153 and -47 were the dominant congeners, contributing an average of 40% and 37% respectively, to the average ΣPBDE congener profile. The remaining PBDE content came from BDEs -100, -99 and -28 with average contributions

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of 12%, 8.5% and 2.6% respectively. BDEs -154 and -183 were not detected in any of the samples. The dominance of BDEs -47 and -153 in human serum is consistent with much of the previous literature including previous measurements of serum from the UK, USA (Sjödin et al., 2004, Sjödin et al., 2008), Japan (Akutsu et al., 2008), Greece (Kalantzi et al., 2011), Romania (Dirtu et al., 2006) and France (Brasseur et al., 2014).

3.1 Demographic trends: Age, Weight and BMI

Despite the narrow age range of participants (23-42 years), Figure 1 suggests that there is a decrease in HBCDD levels with age (R^2 = 0.105). However, a linear regression analysis shows this to be insignificant (p = 0.08). There were no observed associations between PBDE levels of participants and their age. This may be due to the limited sample size and age range of participants in the study. Previous studies have demonstrated higher levels of PBDEs in children and infants (Toms et al. 2009), however this study only investigated mothers of child-bearing age.

A linear regression suggested a weak positive association between HBCDD levels and bodyweight of the participant (R^2 = 0.075, p = 0.036; Figure S1a). However, when corrected for height by using BMI instead of weight (Figure S1b), this association was no longer significant (R^2 = 0.057, p = 0.068). There were no observed associations between bodyweight or BMI and PBDE levels in participants from this study.

3.2 Temporal Trends: Exposure in the United Kingdom

Data on human exposure to HBCDDs in the UK is scarce, with only two previous studies measuring breast milk concentrations from samples collected between 2008 and 2011 (Harrad and Abdallah, 2015, Abdallah and Harrad, 2011), and prior to legislative ban. Median ΣHBCDD concentrations from this study (1.8 ng/g lipid, 2014) were significantly lower (ANOVA, p<0.0001) than samples from 2008-2010 and 2010-2011 (3.8 and 5.2 ng/g lipid, respectively) (Abdallah and Harrad, 2011, Harrad and Abdallah, 2015). A recent study of

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breastmilk from 10 women in UK collected in 2014-2015 by Tao et al. (2017) reported similar HBCDD levels as the serum measures in our study (median: 2.9 ng/g lipid, range: 0.7-7.1 ng/g lipid) (**Figure 2**). This is suggestive of a temporal trend to decreasing HBCDD exposure in UK women. While there is some precedent for comparing serum and breast milk biomarker concentrations as indicative of overall body burden, the samples were collected over a relatively short period of time (2008 to 2015, across the 4 different studies), for a comprehensive temporal assessment of exposure. Furthermore, HBCDDs were only subject to legislative bans in 2013 – one year before samples were collected for this study (Health and Environment Alliance, 2013), meaning that it is too early to assess the impact of legislative action on HBCDD exposures in the UK population.

The range of ΣPBDE concentrations in this study are similar to those found in Newcastle-Upon-Tyne, UK in the same year (1.0-16 ng/g lipid (Bramwell et al., 2014)) and from Birmingham in 2010, 2010-11 and 2014-15 (Abdallah and Harrad, 2014, Harrad and Abdallah, 2015, Tao et al., 2017). Median ∑PBDE concentrations are approximately 3 times lower than those found in serum (5.6 ng/g lipid (Thomas et al., 2006)) and breast milk (6.3 ng/g lipid (Kalantzi et al., 2004)) collected from Lancaster and London from 2001 to 2003 (**Figure 3**). This would suggest PBDE levels have fallen since the 2004 bans of Penta- and Octa- BDE in the EU (Birnbaum and Staskal, 2004). However, breastmilk samples collected in 2014-15 by Tao et al. (2017) contradict this finding with median concentrations of 5.8 ng/g lipid. This is likely due to small sample size (n=10), and high variability both between-individuals, and between geographical regions of the UK. However, it is pertinent to note that in our study, there was a 95% detection rate of PBDEs in UK human serum 8 years after these bans, and Tao et al. (2017) had a 100% detection rate in human milk more than a decade later. This demonstrates that UK populations are still continuously exposed to PBDEs despite legislative

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bans, and further action may be required to reduce body burden at the population level. Similar temporal declines over a period of 10 years have also been suggested for HBCDDs in Australia (Drage et al., 2017), (Toms et al., 2012), and Canada (Ryan and Rawn, 2014), however both compounds are still regularly detected in humans highlighting the need for constant monitoing of their concentrations in humans and the environment.

3.3 Comparison with global biomonitoring data

Literature of serum measures of HBCDD is scarce, however there are a number of studies reporting HBCDDs in milk from various countries (Table 1). The average concentration of HBCDDs from this study (2.2 ng/g lipid) is at the lower end of the range of concentrations found across the world (not detected – 43 ng/g lipid) and half the average concentration worldwide (4.6 ng/g lipid). Concentrations were similar to breast milk collected in Canada in 1992-2005 (Ryan and Rawn, 2014) and serum from Belgium in 2007 (Roosens et al. 2009), whilst they were 3-10 times higher than milk collected from the Philippines in 2008 (Malarvannan et al. 2013b), and India in 2009 (Devanathan et al. 2012). Furthermore, Sahlström et al. (2014) did not detect HBCDD in any serum collected from 48 individuals in Sweden between 2009 and 2010. Average HBCDD concentrations in serum collected in South Korea from 2009-2010 (Kim and Oh, 2014) was approximately 4 times higher than serum from this study, whilst milk collected in Spain from 2006-2007 was almost 20 times higher (Eljarrat et al 2009).

Human biomonitoring studies for PBDEs are more prevalent in the literature than for HBCDDs. The mean ∑PBDE (2.4 ng/g lipid) concentration from this study was at the lower end of the range of ∑PBDE levels measured between 2009 and 2015 internationally (Table 2), but similar to (lipid normalised) ∑PBDE concentrations of breastmilk and serum from other

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regions of the UK ((Bramwell et al., 2014, Tao et al., 2017, Harrad and Abdallah, 2015), Norway (Cequier et al., 2015), Denmark (Vorkamp et al., 2014), and some regions of China (Wu et al., 2017, Wang et al., 2016). Serum levels of ∑PBDEs in this study were approximately 2.5 times higher than breastmilk from Sweden (Darnerud et al., 2015), but between 3 and 20 times lower than serum collected across USA (Watkins et al., 2011, Butt et al., 2016, Makey et al., 2014, Zota et al., 2013, Hurley et al., 2017). Furthermore, serum from 6 individuals in Laizhou Bay, China, with no known occupational exposure were up to 300 times higher than from this study (Wang et al., 2014).

Major strengths of this study include relatively large sample size (59) as well as the the pairing of BFR body burdens with demographic data such as age, weight and height. A potential weakness of the study is the fact that all participants were undergoing *in vitro* fertilisation. However, this was overcome by the fact that they were an otherwise normal population, and patients with any known conditions were excluded from the study, making it an otherwise normal population.

4.0 Conclusions

Here we present data confirming that reproductive aged women from the UK continue to be exposed to both HBCDDs and PBDEs. Data from this study suggests that HBCDD levels decrease with age, however further sampling of a wider age range would be required to further investigate this. It also suggests a positive association between bodyweight and HBCDD levels, which likewise requires a large-scale study to confirm this. The data suggests that 10 years after their European ban, PBDE body burden has begun to decrease in the UK. Whilst it is too early draw any firm conclusions for HBCDDs, they appear to be following a similar pattern to PBDEs, with levels decreasing by a factor of >2.5 since 2010, a trend that has also been

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observed in Australia. Whilst human body burdens appear to be decreasing, both PBDEs and HBCDD are still consistently detected in human serum, despite legislative action limiting their production and use, and highlighting the need to continuously assess human exposure and the effectiveness of policy aimed at reducing exposure.

Acknowledgements

Amy L. Heffernan receives funding support from the Australian Research Council (ARC) and the National Health and Medical Research Council (APP11069); Jochen F. Mueller is funded by an ARC Future Fellowship (FF120100546);

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Figures and Tables

Table 1: Summary population characteristics

Number of participants	59
Age (years)	32
	23-42
Height (cm)	165
	148-191
Weight (kg)	70
	(50-108)
BMI	
Normal (18.5-24.9)	22
Overweight (25-29.9)	32
Obese (30-34.9)	5
Pregnancy status	
Nulliparous	42
Primiparas	6
Miscarried/terminated	11
Smoking status	
Regular smoker	6
Non-smoker	53

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Table 2 ∑HBCDD concentrations (ng/g lipid) in humans from this study and other studies internationally from 2002-2015

Country	Matrix	n	Mean	Range	Ref
Europe					
UK	Serum	59 individuals	2.2	<0.3 - 12.6	This Study
UK	Milk	10 individuals	3.2	0.7 - 7.1	Tao et al. (2017)
UK	Milk	25 individuals	5.95	1 - 22	Abdallah and Harrad (2011)
UK	Milk	10 individuals	6.5	0.3 - 21	Harrad and Abdallah (2015)
Belgium	Serum	16 individuals	2.9	<0.5 - 11	Roosens et al. (2009)
Belgium	Milk	1 pooled sample	1.5	n/a	Colles et al. (2008)
Czech Republic	Adipose	98 individuals	1.2	<0.5-7.5	Pulkrabova et al. (2009)
France	Milk	26	n/a	<1-5	Antignac et al. (2006)
France	Adipose	26	n/a	1-3	Antignac et al. (2006)
Greece	Serum	61 individuals	3.39	0.49-39	Kalantzi et al. (2011)
Ireland	Milk	11 pools	3.5	1.7-5.9	Pratt et al. (2013)
Netherlands	Cord Serum	12	0.2	0.2-4.3	Meijer et al. (2008)
Netherlands	Serum	91	0.2	0.1-0.36	Peters (2004)
Norway	Milk	10 individuals	n/a	nd-0.13	Polder et al. (2008a,b)
Norway	Milk	393 individuals	1.7	<0.2-31	Thomsen et al. (2009a)
Norway	Milk	12 individuals	n/a	0.25-2	Thomsen et al. (2003)
Norway	Milk	85 individuals	n/a	0.4-20	Thomsen et al. (2005)
Norway	Milk	67 Individuals	n/a	nd-3	Thomsen etal. (2009b)
Norway	Milk	193 individuals	1.1	0.1-31	Eggesbø et al. (2011)
Russia	Milk	23 individuals	0.71	nd-1.67	Polder et al. (2008a)
Russia	Milk	14 individuals	0.47	nd-1.15	Polder et al. (2008a)

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Spain	Milk	33 individuals	43	<LOQ-190	Eljarrat et al. (2009)
Sweden	Milk	14 pools	n/a	0.1-0.6	Fangstrom et al. (2008)
Sweden	Milk	204 individuals	n/a	0.09-10	Glynn et al. (2011)
Sweden	Serum	50 individuals	0.46	<0.24-3.4	Weiss et al. (2006)
Sweden	Serum	48 individuals	0	not detected	Sahlström et al. (2014)
Asia					
India	Milk	55 individuals	0.53	<0.05 - 13	Devanathan et al. (2012)
China	Milk	103 individuals	4.29	<LOQ-78	Shi et al. (2013a)
China	Serum	42 pools	0.86	<LOQ - 7.2	Shi et al. (2013b)
China	Milk	12 individuals	2.2	<LOQ - 5.5	Shi et al. (2013b)
Philippines	Milk	33 individuals	0.86	0.13 - 3.2	Malarvannan et al. (2009)
Philippines	Milk	30 individuals	0.21	<0.01-0.91	Malarvannan et al. (2013b)
South Korea	Serum	76 individuals	8.6	<dl-166	Kim and Oh (2014)
Vietnam	Milk	9 individuals	n/a	0.07 - 1.4	Tue et al. (2010)
Vietnam	Milk	4 individuals	n/a	0.11 - 0.97	Tue et al. (2010)
Africa					
South Africa	Milk	28 individuals	0.55	<0.23 - 1.4	Darnerud et al. (2011)
North America					
Canada	Milk	8	3.8	0.4-19	Ryan et al. (2006)
Canada	Serum	59 pools	1	0.33 - 8.9	Rawn et al. (2014)
Canada	Milk	34 individuals	1.8	0.1-28	Ryan and Rawn (2014)
USA	Milk	9	0.5	0.2-0.9	Ryan et al. (2006)
Oceania					
Australia	Serum	63 pools	3.1	<0.5-36	Drage et al. 2017
Australia	Milk	12 pools	6.6	<LOQ - 19	Toms et al. (2012a)
Australia	Serum	40 pools	0.45	<0.1-1.9	Drage et al. 2019

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Table 3 ∑PBDE concentrations (ng/g lipid) in humans from this study and other studies internationally from 2009-2015

Country	Year	Matrix	n	Mean	Median	Range	Ref
Europe							
UK	2014	Serum	59 individuals	2.4	1.9	<0.2 - 15	This Study
UK	2012	Serum	20 individuals	N/A	2.4	42370	Bramwell et al. 20
UK	2012	Milk	8 individuals	N/A	4.8	46753	Bramwell et al. 20
UK	2010	Milk	25 individuals	5.9	5	0.2 - 26	Abdallah & Harra 2014
UK	2010-11	Milk	10 individuals	5.1	3.7	1.3 - 13	Harrad & Abdalla 2015
UK	2014-2015	Milk	10 individuals	6.5	5.8	1.7 - 14	Tao et al. 2017
Denmark	2011	Serum	100 individuals	7.7	7.7	<LOQ - 18	Vorkamp et al. 20
Norway	2012	Serum	46 individuals	3.6	2.3	0.1 - 23	Cequier et al. 201
Sweden	2010	Milk	3 pools	0.73	0.77	0.58 - 0.84	Darnerud et al. 20
Asia							
China	2011	Serum	12 pools	190	N/A	80-780	Wang et al. 2014
China	2012	Serum	6 individuals	N/A	13	4.3 - 42	Chen et al. (2014
China	2013	Serum	10 pools	25	26	13 - 41	Li et al. 2017
China	2014	Serum	32 individuals	7.8	5.6	1.1 - 39	Wang et al. 2016
China	2014	Serum	9 individuals	5.6	N/A	0.42 - 27	Wu et al. 2017
North America							
USA	2009	Serum	31 individuals	28	N/A	3.5 - 350	Watkins et al. 201
USA	2008-2010	Serum	43 individuals	28	N/A	0.71 - 250	Butt et al. 2016
USA	2010-2011	Serum	52 individuals	6.2	N/A	0.25 - 97	Makey et al. 201
USA	2011-2012	Serum	36 individuals	52	N/A	N/A	Zota et al. 2013
USA	2011-2015	Serum	1253 individuals	23	N/A	N/A	Hurley et al. 201

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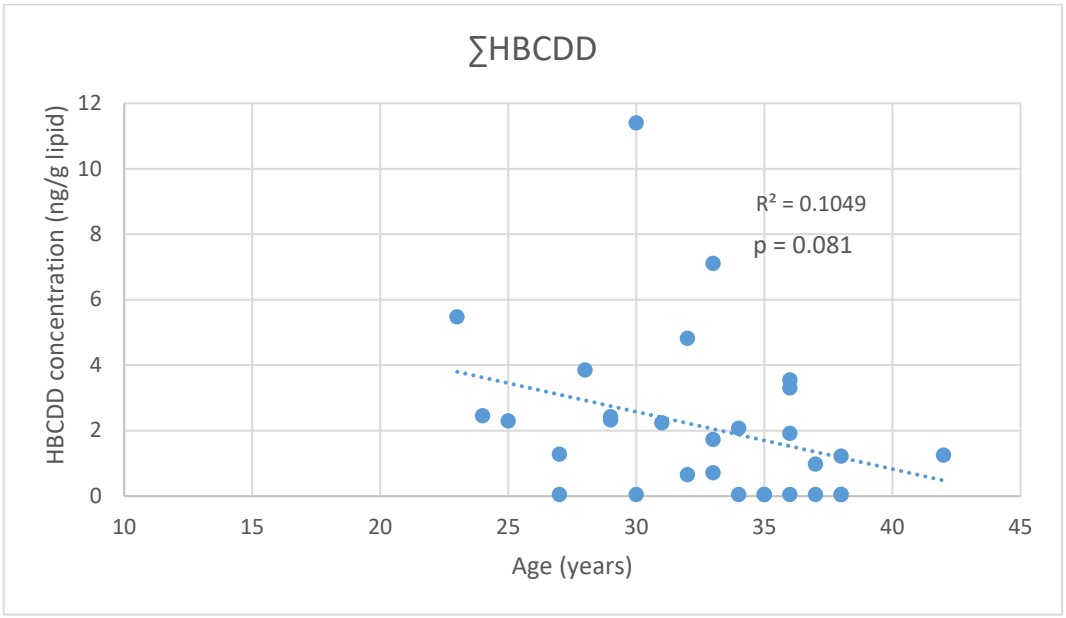
Figure 1 Individual Concentrations (ng/g lipid) of (a) ΣHBCDD and (b) ΣPBDEs vs their age (years)



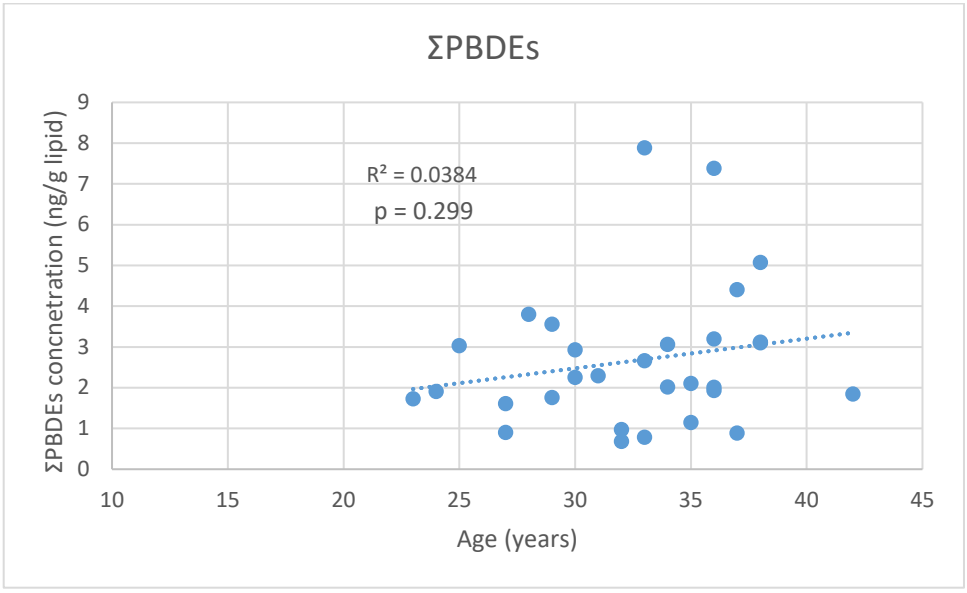


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Figure 2 Temporal variation of mean HBCDD concentrations of serum and breast milk from UK women. Error bar denotes maximum concentration.

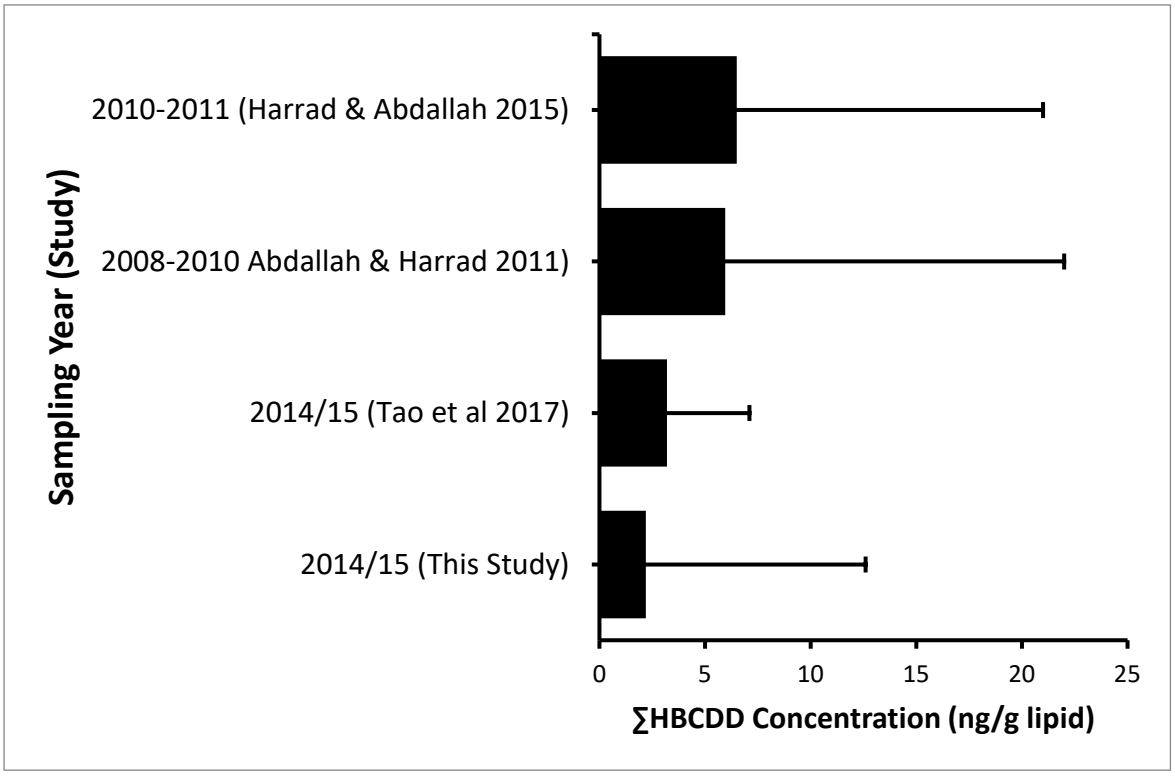

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Figure 3 Temporal variation of mean PBDE concentrations of serum from UK adults from this study and previous studies. Error bar denotes maxium concentration.