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Serum levels of decabromodiphenyl ether (BDE-209) in women from different European countries and possible relationships with lifestyle and diet

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ABSTRACT

To determine possible effects of lifestyle, diet, housing and professional activities on differences in individual levels of decabromodiphenyl ether (BDE-209) in serum of women, 20 to 40 years of age, in The Netherlands, the United Kingdom, Norway and Spain.

BDE-209 was measured in serum of 145 female volunteers with no known occupational exposure from Norway, United Kingdom, The Netherlands and Spain. Blood levels of BDE-209 in a subgroup of 40 Dutch women were determined twice at a six months' interval. An extensive questionnaire was used to obtain detailed information about lifestyle factors that might contribute to BDE-209 exposure. Serum levels were used to determine margin of systemic exposure compared with a 28d rat toxicity study.

Median BDE-209 serum concentrations were highest in The Netherlands and United Kingdom, respectively 8.8 and 9.3 pg/g ww. or 2.6 and 2.8 ng/g lipid. Median levels in Spain and Norway were lower, respectively 7.4 and 5.2 pg/g ww. or 3.3 and 0.8 ng/g lipid. Maximum levels in individual women were higher by one order of magnitude than the mean or median. The country of residence was the only variable significantly associated with BDE-209 levels; we found that the differences between countries could not be explained by any of the investigated exposure variables, and that these did not explain differences between individuals either. No consistent relationships were determined between diets, household, clothes, number and duration of use of electronics and occupational activities for the whole study group.

We could not identify which of the multiple sources of exposure accounted for individual differences in blood levels. Although small differences in mean BDE-209 serum levels were recognized between countries, these differences are unlikely to cause a differential result with respect to risk assessment.

1. Introduction

In modern life, flame retardants have become part of efforts to protect society against injuries, death and economic damage due to fires. A wide range of chemicals have been developed as flame retardants, from which the polybrominated diphenyl ethers (PBDEs) have been commonly used for many decades. Various PBDE products have been in production and use for several decades, commercial PentaBDE, OctaBDE and DecaBDE mixtures comprising diphenyl ethers of varying bromination degree. Some PBDEs have physico-chemical properties that promote environmental persistence and accumulation in food chains and humans (Darnerud et al., 2001; de Wit, 2002; Frederiksen et al., 2009; Tanabe et al., 2008; Zhu et al., 2009). Certain lower brominated congeners have been reported to have long half-lives in humans, wild life and experimental animals, indicating a distinct role of bromine atoms in reducing metabolic rates of these compounds (Geyer

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et al., 2004; Gill et al., 2004; Toms et al., 2009b). As a result, levels of tetra- to heptabrominated BDEs in environmental biota and humans can equal those for PCBs in many industrialized countries (Haraguchi et al., 2009; Hites, 2004; Schecter et al., 2005).

In the European Union, the commercial Penta- and OctaBDE mixtures were taken off the market in 2005 because of adverse effects observed in experimental animals (Directive 2003/11/EC). In North America these commercial formulations were voluntarily withdrawn from the market by industry in 2004 (BSEF, 2009). Further, since May 2009, tetra- to heptabrominated diphenyl ethers have been listed in the UN Stockholm Convention on Persistent Organic Pollutants (http://www.pops.int). In contrast, commercial DecaBDE is still use as flame retardant for plastics and textiles when our study was done (BSEF, 2009; Harrad et al., 2008; Public Health England, 2009; 2013). The commercial mixture consists primarily of the fully brominated diphenyl ether (BDE-209) and smaller amounts of nonabrominated BDE (0.3–21.8%) and octabrominated BDE (0–0.04%). Although its use in electrical and electronic equipment had been banned in the EU in 2008 (BSEF, 2009) and the production and sales of commercial DecaBDE (c-DecaBDE) has been phased out in North America (BSEF, 2016), there is ongoing human exposure from dust in indoor environments (Harrad et al., 2006; Law et al., 2014) and from diet, particularly seafood (Shaw et al., 2009). Presently c-DecaBDE is still under consideration for restriction and elimination under EU's REACH regulation and UN's Stockholm Convention, respectively (http://chm.pops.int/Default.aspx?tabid=5171). In order to evaluate the result of these regulations in reducing human exposure, it is of great importance to establish good biomonitoring data for DecaBDE in particular.

Because of the adverse properties and effects of the lower brominated BDEs, commercial Penta- and OctaBDE have been phased out in European countries in the early 2000s and were globally banned by the UN Stockholm Convention in 2009. As a result, the increasing temporal trends of levels of tetra- to heptabrominated BDEs in human blood and milk have leveled off in the late 1990s in Europe and have declined since, this (Fängström et al., 2008; Thomsen et al., 2007), but is less distinct for North America (Law et al., 2014). Furthermore, an upward trend for decaBDE has been observed in the same time period (Law et al., 2014). It is well established that levels of lower brominated PBDEs in humans may vary strongly among geographical regions, e.g., mean total PBDE levels in North America are about one order of magnitude higher than in Europe (Frederiksen et al., 2009; Fromme et al., 2016; Hites, 2004). In non-occupational situations the relative contribution of decabromodiphenyl ether (BDE-209) in humans constitute a variable part of the total amount of PBDE body burden (Antignac et al., 2009; Frederiksen et al., 2009; Gomara et al., 2007; Thuresson et al., 2005). The geographical differences might partly be explained by different regional fire safety regulations and use of decaBDE containing flame-retardants in consumer products (Harrad et al., 2008). Also, within countries individual differences in PBDE levels can be quite substantial and may easily exceed more than one order of magnitude in human blood and milk (Frederiksen et al., 2009; Hites, 2004).

At present, the cause for this strong variability in human levels is unclear, but lifestyle factors have been suggested as a contributing factor. Although, food is an important pathway for human exposure to PBDEs (Fromme et al., 2009; Meng et al., 2007; Schecter et al., 2006, 2008; Voorspoels et al., 2007; Wu et al., 2007), the ingestion of house dust is also considered to be an important exposure pathway, especially for BDE-209 (Harrad et al., 2006, 2008; Jones-Otazo et al., 2005; Sjodin et al., 2008; Toms et al., 2009a).

Many in vivo toxicokinetic and toxicological studies with PBDEs with different degrees of bromination were done over the last decade to support risk assessment for humans and wildlife (Birnbaum and Cohen Hubal, 2006; Darnerud, 2003; Staskal et al., 2008). As a result, multiple toxic and biological effects have been identified (Darnerud, 2003; He et al., 2009; Kuriyama et al., 2005), which show similarities between the lower brominated PBDEs and decaBDE (Dingemans et al., 2016). These include interactions with the pregnane X (PXR) and sex steroid receptors (Dang et al., 2007; Fery et al., 2009; Mercado-Feliciano and Bigsby, 2008; Pacyniak et al., 2007), steroidogenesis (Canton et al., 2006; Canton et al., 2008) and thyroid hormone homeostasis (Lema et al., 2008; Talsness et al., 2008). In addition, effects on neurodevelopment and behavior in mammalian test systems have been observed for these compounds, including BDE-209 (Viberg et al., 2003, 2006, 2008, 2009a, 2009b); these effects bear similarity with non-dioxin-like PCBs (Eriksson et al., 2006; He et al., 2009). With respect to mechanism of action involvement of metabolites has also been determined for various endpoints such as sex steroid hormone receptors, steroidogenesis (Canton et al., 2006, 2008; He et al., 2008) and regulation and interference with calcium homeostasis in neuronal cells (Alm et al., 2006; Bocio et al., 2003; Dingemans et al., 2008). There is also emerging evidence that exposure to PBDEs in early human life stage can influence endocrine and neurobehavioral development (Sagiv et al., 2015; Harley et al., 2017; Zota et al., 2011). Recently, it has been argued that risk assessment for PBDEs and non-dioxin PCBs should be combined (Dingemans et al., 2016) Earlier studies suggested that PBDEs can have a dioxin-like mechanism of action, but this is now attributed to contamination of commercial PBDE mixtures with brominated dibenzo-*p*-dioxins and dibenzofurans (Luthe et al., 2008; Peters et al., 2004, 2006; Van den Berg et al., 2006).

Many lower brominated PBDEs bioaccumulate in the aquatic and human food chain and in the past, bioaccumulation of BDE-209 was assumed to be low due to the large molecular size, extreme hydrophobicity and low bioavailability (Darnerud et al., 2001; Debruyn et al., 2009; Drouillard et al., 2007; Hardy et al., 2009; Huwe et al., 2008b; Kelly et al., 2008; Shaw et al., 2008). However, recent results from both aquatic and terrestrial food web studies demonstrate that BDE-209 bioaccumulates, i.e., bioaccumulation factors and trophic magnification factors above 1 (Chen et al., 2007, 2008; Law et al., 2006; UNEP, 2015). Further, environmental levels of BDE-209 can be up to lower ppm levels in abiotic compartments like sediment and house dust (Harrad et al., 2008; Song et al., 2005a, 2005b; Xiang et al., 2007; Zegers et al., 2003). Thus, risk assessment of PBDEs is complicated by significant differences among congeners with respect to toxicokinetics, toxicology as well as differences between species, including humans (Birnbaum and Cohen Hubal, 2006). Our present study was conducted to determine systemic exposure via blood of BDE-209 in women in four different European countries (The Netherlands, United Kingdom, Norway and Spain) and to study factors influencing those levels, for example differences in life style and fire safety regulations. So far, there are few systematic studies that have focused on systemic exposure of DecaBDE in residents and their households. Blood samples were collected from a group of volunteers, women 20 to 40 years of age. In view of the uncertainties in human exposure to c-DecaBDE, a questionnaire was designed to obtain broad and specific information regarding possible sources of exposure, including lifestyle, use of electrical and electronic devices, diet and country of residence. This questionnaire was compiled based on the information by the BSEF or EU on the (possible) use of DecaBDE in household products (cf EFSA, 2011). The combined information might explain any individual differences in levels of BDE-209 in serum and elicit the possible manner in which human exposure to c-DecaBDE occurs in non-occupational situations. The present report describes the results of a first study of an originally planned 10-year human monitoring program in Europe that would provide the authorities with insight into the long term serum levels of BDE-209 in humans and possible causal relationships with specific exposure scenarios.

2. Materials and methods

2.1. Blood sampling and data collection

In view of different European dietary and lifestyle factors Norway, Spain and The Netherlands were selected from the Nordic,

Mediterranean and West European Regions. In addition, the United Kingdom was included because of more stringent fire safety regulations compared with the rest of the European Union. A total of 145 women, age 20 to 40 years were recruited to participate in the study. This particular population was chosen in order to determine the range in systemic exposure of women around the (theoretical) age of first pregnancy and the initial first sampling round focused on blood of these women. A requirement for the first round was that no breastfeeding had occurred in the six months prior to sampling, so as to avoid a possible depletion of the body burden due to lactation. Later, it turned out that 15 women did not fulfill this criterion and statistical analyses were done with and without this subgroup.

All volunteers completed a questionnaire that contained questions related to lifestyle, work and diet that might have been related to the exposure to c-DecaBDE. Topics were selected based on the knowledge available at the time of the first sampling with respect to use, exposure and occurrence of c-DecaBDE in the environment and products. The questionnaire is included in the supplementary information.

In all four participating countries, The Netherlands (NL), Norway (NO), United Kingdom (UK) and Spain (ES) the approval of a medical ethical committee was obtained as well as informed consents from the women, before sampling of the blood. By December 2007, the sampling in NO and the NL (first and second round) was completed, while those in ES and the UK were finalized in May and June 2008, respectively. The Institute for Risk Assessment Sciences (IRAS) of Utrecht University, The Netherlands, coordinated this study and was also responsible for the collection of two rounds of serum samples from the same volunteers (n = 40) in The Netherlands with a six-month interval. The interval analyses were done to collect information on variation in time for non-occupational exposed individuals. Collection of the blood samples in the UK (n = 40), Norway (n = 40) and Spain (n = 25) was done respectively by the Institute of Occupational Medicine, (Edinburgh, UK), Division of Environmental Medicine, Norwegian Institute of Public Health (Oslo, Norway) and Municipal Institute for Medical Research (Barcelona, Spain). The Institute for Environmental Studies (VU University, Amsterdam, The Netherlands) analyzed the serum samples for BDE-209 as described below. A detailed protocol of the collection, storage and handling of the blood samples is included in the supplementary information.

2.2. Sample preparation and chemical analysis

BDE-209 was extracted from 5 g of serum using an automated solid phase extraction (SPE) technique, followed by an acid silica column clean up step. Extracts were analyzed by gas chromatography with electron capture negative ionization mass spectrometry (GC/ECNI-MS) using a short DB-5 column (15 m, internal diameter 0.2 mm, film thickness 0.01 mm). Before starting the analysis of samples, multiple blank analyses were performed to ensure a minimal background contamination with BDE-209. For each series of 10 serum samples, several blank analyses (at least three) were performed using calf serum that contained no detectable BDE-209. In each series of 10 samples, one sample was performed in duplicate, demonstrating low variability. Duplicate analyses included samples at very low levels such as 4.1 (s.d. 0.7) and 3.9 (s.d. 0.43) pg/g. ^{13}C-labelled BDE-209 was used as internal standard and serum samples were analyzed at least in duplicate. BDE-209 was quantified using ^{13}C-BDE-209 as internal standard. The recoveries of the ^{13}C decaBDE internal standard were on average 79% (median 76%), with a relative standard deviation of 32%.

Concentrations in serum samples reported have all been corrected for the mean blank value in the control chart at the time the series was analyzed.

The limit of detection (LOD) was calculated as 3 times the standard deviation of the average of blank values. In all sample series, the LOD varied between 3.8 and 4.2 pg/g ww serum.

The limit of quantification (LOQ) was defined as 10 times the standard deviation of the blanks. The LOQ in all series varied between 12.6 and 13.8 pg/g ww serum.

To determine the lipids in the serum samples, cholesterol and triglycerides were measured enzymatically by the Clinical Chemistry Laboratory at the VU Medical Centre. Total lipids (TL) were calculated based on the formula TL (g/l) = 1.12 × CHOL + 1.33 × TG + 1.48 used by Covaci et al. (2006).

2.3. Data analysis

Questionnaire data from all four participating countries were checked intensively, converted to a uniform format where necessary, and merged with serum BDE-209 concentrations into one single dataset. Following the method proposed by Baccarelli and co-workers all samples below the LOD were assigned 1/√2 of the value of the LOD (approx. 2/3 of LOD) (Baccarelli et al., 2005). BDE-209 levels were strongly skewed and therefore log-transformed for statistical analyses to better satisfy the assumptions of normality. Statistical analyses were performed using concentrations on wet weight basis as in vitro and in vivo studies have shown that BDE-209 binds to serum albumin and accumulates primary in plasma and liver and not in fat tissue (Huwe et al., 2008a; Wang et al., 2014).

Statistical analyses were performed using SAS software (SAS System for Windows version 9.1, SAS Institute, Cary, NC). First, BDE-209 levels were tabulated in different categories of the potential explanatory variables. Second, BDE-209 levels were log-transformed before further analysis in view of the skewness of their distribution. Finally, multivariate regression analyses (PROC REG) were done with all potential explanatory variables summarized in groups and in tertiles. The log transformed data in the five data sets were not normally distributed. A Kruskal-Wallis test indicated significant differences. Making a parameter-free comparison using Anova of ranked data and significant difference between Norway and UK (< 0.000), and Norway and NL 2nd round ($p < 0.01$) data sets was detected. Graphpad Prism 6 was used to calculate the Spearman correlation coefficients between the DecaBDE serum levels in the first and the second round from The Netherlands and to construct the Fig. 1.

3. Results

3.1. Serum concentrations of BDE-209

In Table 1 the mean and median serum concentrations based on either on wet weight (ww) or lipid weight (lw) are presented. Only minor differences were observed in median concentrations on a wet weight basis (all within a factor of 2), with UK having the highest (9.8 pg/g ww) and Norway having the lowest (5.2 pg/g ww). The UK and Dutch second round data sets were both statistically significantly higher than the Norway data set ($p < 0.000$ and $p < 0.01$ resp.). No differences among any other data sets were statistically significant. Based on the difference observed between the mean concentrations and the medians, it can be concluded that for all countries positively skewed distributions occur. A noticeable aspect of the individual serum samples was the extreme variation expressed by very high maximum levels, which could easily be one order of magnitude above the mean concentrations. Although mean levels of BDE-209 for UK and The Netherlands were almost similar, respectively 12.6 vs. 12.4 pg/g ww, the highest individual levels of BDE-209 were observed from The Netherlands. This was consistent for both rounds of sampling within a six months' interval in this country. With the limit of detection being around 4 pg/g ww, the highest number of non-detects (38%) was found in samples from Norway (See Table 1 for details). Of all the serum samples analyzed, 75% had BDE-209 concentrations above 5 pg/g ww. In deviation from the original study design, 15 women had ceased breastfeeding less than six months prior sampling. When these women were excluded from the study population the overall pattern between

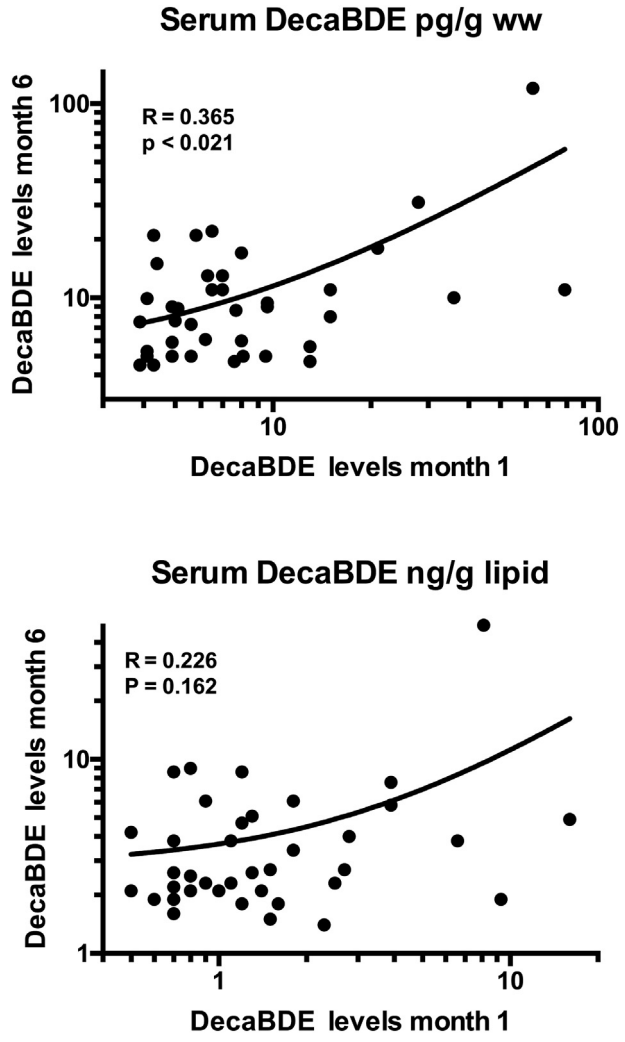

Fig. 1. Possible associations between serum concentrations of BDE-209 (upper panel: pg/g wet weight; lower panel: ng/g lipid weight) measured twice, 6 months apart, in Dutch participants.

Table 1
BDE-209 concentrations in human serum samples (pg/g wet weight and ng/g lipid).

	The Netherlands		Norway	Spain	UK
	Round 1	Round 2			
pg/g serum					
Mean[a]	11.6	12.4	7.3	8.5	12.6
s.d.[a]	15.5	18.5	9.5	4.5	9.7
Median	6.5	8.8	5.2	7.4	9.3
Minimum	< 3.9	< 4.5	< 3.8	< 4.7	< 4.2
Maximum	79.0	120.0	62.0	19.0	58.0
n	40	40	40	25	40
n < LOD	4	8	15	5	2
ng/g lipid					
Mean[a]	2.2	4.6	1.3	3.5	3.5
s.d.[a]	3.0	7.6	1.8	1.9	4.7
Median	1.2	2.6	0.8	3.3	2.8
Minimum	< 0.7	< 1.5	< 0.5	< 0.8	< 0.8
Maximum	16.0	49.1	11.8	7.7	28.8
n	40	40	40	25	39
n < LOD	4	8	15	5	2

[a] Non-detects have been included in the calculation of the mean and s.d. as LOD/√2.

Table 2
Mean serum concentrations of BDE-209 in individuals in relation to different types of diets.

	Mean (s.d.) pg/g ww	Mean (s.d.) ng/g lw
Type of diet		
Normal diet (N = 128)	10.0 (10.8)	2.4 (2.5)
Vegetarian with fish (N = 4)	20.2 (25.3)	8.1 (13.8)
Strictly vegetarian (N = 3)	16.8 (7.9)	3.7 (1.0)
Veganist (N = 1)	4.9	0.7
Other (N = 4)	6.8 (1.2)	1.8 (1.0)
Egg consumption		
Never (N = 7)	17.9 (19.9)	7.0 (10.5)
< 1/week (N = 51)	8.5 (5.6)	2.1 (1.8)
1–2/week (N = 75)	10.6 (11.7)	2.5 (2.4)
3–5/week (N = 7)	4.5 (2.3)	1.2 (1.1)
6–7/week (N = 4)	21.4 (27.3)	4.1 (5.1)
Food consumption (milk, fish, shellfish, meat, eggs) in tertiles		
Low (N = 41)	11.4 (10.3)	3.1 (4.7)
Medium (N = 55)	9.1 (9.3)	1.9 (1.8)
High (N = 47)	10.5 (13.7)	2.9 (3.0)

N = Number of samples within each category.

Table 3
Mean serum concentrations of BDE-209 in individuals in relation to the use of electronic equipment.

	Mean (s.d.) pg/g ww	Mean (s.d.) ng/g lw
Number of TV's		
0 (N = 6)	12.0 (11.9)	2.8 (2.1)
1 (N = 90)	9.5 (9.7)	2.5 (3.6)
2 (N = 27)	10.7 (14.4)	2.6 (3.1)
3 (N = 13)	10.3 (4.9)	2.9 (2.2)
4 or more (N = 8)	14.4 (19.9)	2.5 (2.5)
Number of coffee makers & water kettles		
0 (N = 20)	15.5 (16.7)	5.4 (6.2)
1 (N = 77)	8.8 (5.5)	2.3 (2.0)
2 or more (N = 47)	10.2 (14.3)	1.8 (2.5)
Number of dishwashers		
0 (N = 74)	12.0 (13.3)	2.9 (4.2)
1 (N = 70)	8.3 (7.9)	2.2 (1.9)
Hours of use TV and computers in tertiles		
Low (< 120 h; N = 42)	11.4 (13.1)	3.1 (4.9)
Medium (120–210 h; N = 46)	10.6 (11.8)	2.5 (2.7)
High (> 210 h; N = 47)	9.3 (9.6)	2.1 (1.9)
Hours of use radio and CD/DVD/Video in tertiles		
Low (< 25 h; N = 47)	8.3 (4.6)	2.1 (1.8)
Medium (25–50 h; N = 45)	9.9 (10.3)	2.4 (2.8)
High (> 50 h; N = 47)	12.2 (15.6)	3.1 (4.7)
Number of other electrical apparatuses (microwave, coffee maker, electrical water kettle, blender, oven, dishwasher, washer, dryer, vacuum cleaner)		
Low (1–5; N = 39)	12.2 (13.2)	3.3 (4.8)
Medium (6–7; N = 58)	9.4 (6.2)	2.4 (2.2)
High (8–11; N = 48)	9.6 (13.7)	2.1 (2.7)

N = Number of samples within each category.

countries did not change significantly, with the UK still having the highest mean levels of BDE-209, closely followed by The Netherlands and with Spain and Norway having the lowest levels (data not shown).

3.2. Variables explaining individual variability of BDE-209 levels

There were no meaningful correlations between BDE-209 levels and any of the dietary variables (Table 2), use of electronic equipment (Table 3) or use of synthetic clothing (Table 4). The type of diet was examined for its influence on the BDE-209 serum levels (Table 2). Most women (n = 128) reported having a normal diet including meat, with

Table 4
Mean serum concentrations of BDE in individuals in relation to the use of synthetic and natural clothes.

	Mean (s.d.) pg/g ww	Mean (s.d.) ng/g lw
Use of synthetic blouses		
1: 100% natural materials (*N* = 29)	15.1 (14.8)	4.1 (5.6)
2 (N = 42)	7.5 (4.9)	2.0 (1.9)
3 (N = 51)	10.5 (13.4)	2.5 (2.9)
4 (N = 18)	8.6 (4.8)	1.9 (1.4)
5: 100% synthetics (N = 4)	5.4 (2.2)	1.5 (1.0)
Use of synthetic clothes (underwear, pants, blouses, socks) in tertiles		
Low (sum score 4–7; N = 38)	13.7 (13.4)	3.4 (5.0)
Medium (sum score 8–9; N = 45)	8.0 (5.5)	2.1 (1.9)
High (sum score 10–17; N = 61)	9.6 (12.3)	2.3 (2.7)

N = Number of samples within each category.

only few individuals being vegetarian. The type of diet (normal, vegetarian, vegan) did not show any statistically significant association with BDE-209 levels. However, mean serum concentrations of vegetarians with or without fish consumption (n = 7) were somewhat higher than those with a normal diet (See Table 2 for details), but this was not statistically significant. The possible influence of specific dietary components was also taken into account, but no statistically significant contribution of eggs, dairy products, fish or meat could be established (Table 2).

We also investigated if the presence or use of electronic equipment in the household was related to the individual serum concentrations (See Table 3 for more details). No correlations were found with any type of equipment, except for coffeemakers and electric water kettles. With respect to the duration electronic equipment was used some positive trends were observed, e.g. hours of use of TV's, radio's and CD/DVD/video player, but none of these were statistically significant (Table 3).

The type of materials used in the living and bedroom and in clothes (natural vs. synthetic) was also included as covariate to explain individual differences in serum levels. While the abundance of synthetic material on floors or in furniture did not explain any variability in BDE-209 levels, it was observed that the use of synthetic fabric in clothes appeared to be associated with approximately 25% lower serum levels of BDE-209 compared to natural clothes. For these comparisons the mean serum levels in Norwegian women, being the lowest in the study, were used as a base line (See Table 4 for details)

The multivariate regression analyses results are shown in Table 5 which contains the variables that have been studied in relation to clothing, electronic appliances, diet and parity. Compared to low exposed Norwegian women, BDE-209 levels were significantly higher in the UK when expressed in pg/g wet weight, and significantly higher in the UK and Spain when expressed in ng/g lipid weight. Use of synthetic clothes was associated with lower BDE-209 levels when expressed in pg/g wet weight but not when expressed in ng/g lipid weight.

For the group of Dutch participants, serum concentrations from two rounds of blood sampling were included in the study to examine individual differences within a six months' time interval (Table 1). The serum concentrations (wet and lipid weight) were plotted against each other on a logarithmic scale in Fig. 1. These relationships were only (weakly) statistically significant ($p < 0.02$) for the wet weight analyses, which indicates that serum levels of DecaBDE within an individual can vary significantly over a six months' time period.

Table 5
Multivariate analysis of geometric means of BDE-209 concentrations in A) pg/g wet weight and B) ng/g lipid weight.

A		95% confidence interval
Baseline = geometric mean serum BDE-209 pg/g wet weight in Norwegian women	7.7	5.0–11.9
	Ratio to baseline	
Netherlands	1.42	0.98–2.06
UK	**1.74**	**1.19–2.53**
Spain	1.45	0.97–2.23
Milk, fish, shellfish meat & eggs, 2nd tertile	0.97	0.74–1.30
Milk, fish, shellfish meat & eggs, 3rd tertile	1.03	0.72–1.48
Television & computer use, 2nd tertile	1.07	0.81–1.40
Television & computer use, 3rd tertile	0.91	0.68–1.23
Radio, CD, DVD & video use, 2nd tertile	0.93	0.70–1.22
Radio, CD, DVD & video use, 3rd tertile	1.01	0.75–1.34
N of other electric appliances, 2nd tertile	0.93	0.71–1.25
N of other electric appliances, 3rd tertile	0.93	0.68–1.28
Use of synthetic clothes, 2nd tertile	**0.72**	**0.53–0.99**
Use of synthetic clothes, 3rd tertile	**0.73**	**0.55–0.98**
Having children, yes vs. no	0.96	0.65–1.40

B		95% confidence interval
Baseline = geometric mean serum BDE-209 ng/g lipid weight in unexposed Norwegian women	1.39	0.86–2.25
	Ratio to baseline	
Netherlands	1.41	0.94–2.12
UK	**2.47**	**1.65–3.71**
Spain	**3.68**	**2.30–3.78**
Milk, fish, shellfish meat & eggs, 2nd tertile	0.89	0.65–1.22
Milk, fish, shellfish meat & eggs, 3rd tertile	1.14	0.76–1.69
Television & computer use, 2nd tertile	1.02	0.75–1.39
Television & computer use, 3rd tertile	0.90	0.65–1.25
Radio, CD, DVD & video use, 2nd tertile	0.96	0.70–1.30
Radio, CD, DVD & video use, 3rd tertile	1.03	0.75–1.41
N of other electric appliances, 2nd tertile	0.85	0.62–1.17
N of other electric appliances, 3rd tertile	0.88	0.62–1.24
Use of synthetic clothes, 2nd tertile	0.85	0.60–1.19
Use of synthetic clothes, 3rd tertile	0.76	0.56–1.05
Having children, yes vs. no	0.81	0.53–1.24

Bold: statistically significant at $p < 0.05$.

4. Discussion

4.1. Results in global context

Of the three commercial PBDE mixtures only one, c-DecaBDE, is still applied as a flame retardant. This study describes BDE-209 serum levels in women from four different European countries, aged 20–40 years, who were non-occupationally exposed. Samples were collected between mid 2007 and mid 2008. Median serum concentrations were in the same range in all four countries, between 5 and 10 pg/g ww. Nevertheless, subtle differences were observed and the country of residence contributed most to the variation in BDE-209 serum concentrations of all factors examined. The highest concentrations were found in the UK and The Netherlands with mean serum levels around 12.5 pg/g ww or 2.2 to 3.5 ng/g lw. The apparent lack of a real difference in serum levels between both countries is notable, as the UK has stricter national fire safety regulations, comparable with that in some US states (Harrad et al., 2008). UK and Dutch BDE-209 serum levels in the present study are slightly higher than mean or median concentrations in other studies from Europe, e.g. France, Spain, Norway and Sweden (Antignac et al., 2009; Frederiksen et al., 2009; Gomara et al., 2007; Thuresson et al., 2005). Median BDE-209 levels from Spain determined in this study are three fold higher than those reported earlier from this country (Gomara et al., 2007), but still in the very low ng/

g lw range. Median serum levels of BDE-209 from Norway were around 1.5 ng/g lw (Thomsen et al., 2008), which is almost one order of magnitude lower than those determined in pooled serum samples from the period 1998 to 2003 (Thomsen et al., 2007), but rather similar as those reported from Sweden (Hites, 2004). In a French study, median concentrations of BDE-209 in women were in the same range as in our study, respectively 5.8 versus 1 to 4 ng/g lw. (Antignac et al., 2009). BDE-209 blood levels reported in one study for the U.S. are in the same range as those observed in our study (Schecter et al., 2005). This observation is in contrast with mean blood levels of the lower brominated PBDEs, which can be one order of magnitude higher as those in Europe (Hites, 2004; Schecter et al., 2005). This noticeable difference between both continents has been explained by the significantly higher use of commercial PentaBDE and OctaBDE mixtures in North America in the past, while the use of c-DecaBDE is in the same range for both continents (Harrad et al., 2004; Hites, 2004). Several studies from Japan and China have reported BDE-209 levels in blood from non-occupational exposed individuals. In Japan the mean or median blood levels were similar to our study, around 1 to 7 ng/g lw. (Inoue et al., 2006; Kawashiro et al., 2008). However, two studies from China reported serum levels that were on average one to two orders of magnitude higher than in our study (Jin et al., 2009; Zhu et al., 2009). One of these studies reported the levels in residents living close to a BDE-209 production area (Jin et al., 2008) and further investigations are needed to clarify whether these results are indeed representative for general background exposure in China. Mean serum levels of BDE-209 in Australia are in the same range as those observed in our study (Toms et al., 2009b). For a more detailed recent analysis of global temporal and spatial time trends see Law et al. (2014).

4.2. Possible DecaBDE sources

In our study, consumption frequencies of major food groups were included as a possible contributing factor to differences in serum levels of BDE-209, but no association with any type of food was found. A vegetarian diet with or without fish was associated with some higher, but not statistically significant, serum levels in our study (Table 2). However, as our study included only 7 participants on a vegetarian diet and therefore it may well be that this observation is underpowered to detect a statistical association. Possibly, the consumption of eggs could have contributed slightly to the observed levels in our study, but a consistent relationship was not observed (Table 3). Studies from Belgium and the US indicate that BDE-209 can be a common contaminant in eggs (Covaci et al., 2009; Schecter et al., 2006), but our study did not unequivocally confirm this as a major contribution to exposure of our volunteers.

BDE-209 may easily enter the home as an additive frequently used in household electronic equipment, carpets and furniture upholstery. As house dust has been established as a major source for human exposure to PBDEs, including DecaBDE, it may very likely originate from these household articles (Harrad et al., 2008; Jones-Otazo et al., 2005; Sjodin et al., 2008; Stapleton et al., 2005). We did not detect any statistically significant correlation between serum BDE-209 levels and the number of electronic devices nor duration of their use in the households of the participants (Table 3). Serum levels of BDE-209 in our multi-country study are much lower than those of workers in electronic waste dismantling facilities, who have serum levels that are one to two orders of magnitude higher than observed in individuals with only background exposure (Bi et al., 2007; Jakobsson et al., 2002; Thuresson et al., 2005). The contact with electronic equipment for our study population should also be considered as common.

The abundance of textiles in households, e.g. carpets and upholstery, was also used in the analysis of variance for the whole study population, but again no relationship with serum levels could be found in our study. The use of synthetic clothing was included as an exploratory parameter in our study, because the use of flame retardants in their production process is unknown (*pers. comm. BSEF*). However, no relationship was found between the use of synthetic clothing and DecaBDE blood levels (See Table 4). A study from California reported high levels of lower brominated PBDEs in house dust suggesting this as an explanation for the observed high serum levels in Californian populations. However, it should be noted that a limitation of this study is the lack of direct comparison of individual serum levels and dust from the same household at the time of sampling (Zota et al., 2008).

For the Dutch participants, BDE-209 concentrations were measured in two separate serum samples collected with a six months' time interval. A low, but statistically significant correlation between both results was observed. A possible explanation for this could be the relative short half-life (~two weeks) found in humans for BDE-209 (Thuresson et al., 2005; Thuresson et al., 2006) where fluctuations in exposure may change body burdens within the six-month period considerably. With such relatively short half-life fluctuations in exposure to specific (unknown) point sources could easily and significantly change body burdens within the six months' time period.

4.3. Implications for human health

The question can be raised to which extent our observed serum levels of BDE-209 in these female volunteers can be compared with results from experimental toxicity studies. In a review of the toxicology and human health risks of BDE-209, a significant number of toxicity studies were evaluated (Hardy et al., 2009). Three studies with endpoints on liver, spleen, maternal and developmental toxicity were used to determine a reference dose (RfD) of 4 mg/kg-day (Hardy, 2002; NTP, 1986; Silberberg et al., 2009). This RfD value is similar to the one determined by the National Academy of Sciences (NAS) using the NTP study (NTP, 1986). In contrast, the US EPA derived a much lower RfD of 0.007 mg/kg-day (EPA, 2008), but its derivation has been the subject of scientific debate (Goodman, 2009; Hardy et al., 2009). If these RfD values are used in combination with a recent estimate for background dietary intake of 1–5 ng/kg-day in Europe (EFSA, 2011; Frederiksen et al., 2009; Fromme et al., 2009; Knutsen et al., 2008; Lorber, 2008), a margin of exposure (MOE) between 1.4 and $800*10^3$ would be calculated. However, this range of MOE does not take into account other routes of exposure e.g. ingestion of house dust, which might be especially relevant for children due to their increased hand-to-mouth activity (Stapleton et al., 2012). Recently, adult exposure to PBDEs, including BDE-209, in the US was summarized and the daily uptake was estimated to be about 2 ng/kg/day for an adult of 70 kg. Daily intake for US children aged 1–5, 6–11 and 12–19 years was estimated significantly higher, respectively 49, 14 and 9 ng/kg/day (Lorber, 2008). Even with the higher infant exposure levels the MOE with the RfD still remains above a factor 100. However, if the maximum serum levels reported in our study are considered, this MOE could be approximately a factor of 10 lower.

Our study did not focus on uptake but blood levels of BDE-209, which would be a better proxy for systemic concentrations observed in experimental studies. The only animal study so far which has calculated systemic concentrations of BDE-209 in plasma on lipid weight basis in relation to observed effects, is a subchronic 28-days study with rats (van der Ven et al., 2008a; Van der Ven et al., 2008b). The hepatic benchmark dose levels (BMDLs) for the most sensitive effect was converted to a plasma level of 1.5–3.2 μg/g lw. Assuming comparable levels in serum and plasma on a lipid basis for BDE-209 (Frederiksen et al., 2009), this can be used for a comparison with our study. Using a mean and median serum concentration of 1–5 ng/g lw it provides a MOE for these women of approximately 300 to 3000 compared with the benchmark dose derived from the rat study. However, our study also indicates that in this non-occupationally exposed group of women maximum serum concentrations could be up to one order of magnitude above the mean or median serum concentrations in which case the MOE with the BMDL from the rat study would be lower than 100. Such a situation can also

occur for occupational exposed individuals who may have BDE-209 blood levels one to two orders of magnitude higher than those found in background exposed populations. Theoretically, a comparison between human blood levels and experimental rat data should provide fewer uncertainties for risk assessment, but it has to be recognized that the bench mark dose derived from this 28-day rat study for BDE-209 has been criticized from a methodological point of view with respect to the computational model used (Hardy et al., 2008; van der Ven et al., 2008a; Van der Ven et al., 2008b).

With respect to risk assessment and an MOE derived solely for BDE-209 it should also be recognized that human exposure is not confined solely to BDE-209, but also to other PBDE congeners. It has been estimated that BDE-209 exposure in adults may contribute only 20 to 30% of total PBDE exposure (Fromme et al., 2009; Lorber, 2008). It can therefore be discussed whether or not risk assessment should be based on single congeners only, such as BDE-209, or on the whole mixture of congeners. A number of experimental studies indicate similar mechanisms of action for different PBDE congeners (Canton et al., 2006; Fery et al., 2009; Pacyniak et al., 2007; Sanders et al., 2005; Viberg et al., 2006), which could provide an argument for using the complete PBDE mixture in the risk assessment proposing additivity as default method. Clearly such a mixture approach would have influence on the risk assessment compared with that based on individual congeners.

Finally, the question can be asked to which extent the observed serum concentrations in the female participants of our study would be related to the levels in their breast milk, as all these women were in childbearing age. Several studies have shown that there is a discrepancy between lipid adjusted BDE-209 concentrations in serum and milk, with breast milk levels being about one order of magnitude lower (Darnerud et al., 2015; Frederiksen et al., 2009). To perform a risk assessment of BDE-209 exposure for breastfed infants, concentrations in breast milk as well as maternal blood should be investigated in future studies. In view of the usually higher sensitivity of the fetus, neonate and infants to organohalogen compounds, breastfeeding women should be given priority in future studies with BDE-209 to determine the MOE in relation to experimental studies.

5. Conclusions

The present study determined concentrations of BDE-209 in serum from women aged 20–40 years in The Netherlands, UK, Norway and Spain. Samples were collected in 2007–2008 prior to major restrictions on used of commercial DecaBDE. Mean and median serum levels were within the same range for all four groups, around 5–15 pg/g ww or 1–10 ng/g lw. Maximum serum levels were one order of magnitude higher. Lifestyle, type of clothes, diet and professional activities could not explain the individual differences observed in the total study group, but country of residence was a significant predictor. In view of the virtual absence of the role of lifestyle factors, type of household, use of electronic devices, diet and occupational activities in individual serum levels, it is likely that multifactorial exposures from different sources may account for individual differences in blood levels. In view of the established role of house dust for PBDE exposure, future studies should focus on this matrix and blood levels of residents in the same household. If mean serum levels are compared with the most sensitive endpoints in an experimental study the MOE for average exposure is still two to three orders of magnitude. However, this MOE would be one order of magnitude lower for women with the highest serum level observed in our study.

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Appendix A. Supplementary data

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