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Serum concentrations of polybrominated diphenyl ethers (PBDEs) and a polybrominated biphenyl (PBB) in men from Greenland, Poland and Ukraine

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ABSTRACT

Many brominated flame retardants (BFRs)—including polybrominated diphenyl ethers (PBDEs)—have been shown to persist in the environment, and some have been associated with adverse health effects. The aim of the present study was to quantify serum concentrations of common brominated flame retardants in Inuit men from across Greenland, and in men from Warsaw, Poland and Kharkiv, Ukraine. Serum was sampled between 2002 and 2004 from men 19 to 50 years of age. 299 samples were analyzed for BDE-28, 47, 99, 100, 153, 154 and 183 and the brominated biphenyl BB-153 using gas chromatography–high resolution mass spectrometry. BDE-47 and BDE-153 were detected in more than 95% of samples from all three populations. All other congeners, except BDE-154, were detected in more than 70% of samples from Greenland; lower detection frequencies were observed in Polish and Ukrainian samples. Concentrations of individual congeners were 2.7 to 15 fold higher in Greenlandic relative to Polish and Ukrainian men. Geometric mean concentrations of the sum of the most abundant PBDEs of the Penta-BDE commercial mixture (BDE-47, 99, 100, 153 and 154) were 6.1, 1.7 and 0.87 ng/g lipids in the Greenlandic, Polish and Ukrainian men, respectively. Furthermore, significant geographical differences in BFR concentrations were observed within Greenland. Principal component analysis revealed distinct clustering of samples by country of origin. The associations between ΣPBDEs and age were inconsistent, varying from no association in Greenlandic and Polish study populations to a U-shaped relationship in Ukrainians. We report BFR levels for three populations for which sparse biomonitoring data exists.

1. Introduction

Brominated flame retardants (BFRs) are added to a wide variety of construction and consumer products, such as electronics, furniture and carpets, to delay potential ignition and combustion. Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) are important classes of BFRs, first manufactured in the 1960s and 70s. PBDEs largely replaced PBBs after accidental contamination of cattle feed in Michigan, US in 1973–74, which resulted in acute toxicity in cattle, human exposure via consumption of contaminated food products, and adverse health effects including increases in site-specific cancers (Carter, 1976; Fries, 1985; Hoque et al., 1998). There are three main commercial formulations of PBDEs, differing in their

Abbreviations: AMAP, Arctic Monitoring and Assessment Programme; BFR, brominated flame retardant; DF, detection frequency; LOQ, limit of quantification; (P)BB, (poly)brominated biphenyl; (P)BDE, (poly)brominated diphenyl ether.

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bromine content: Penta-BDE, predominantly used in polyurethane foam; Octa-BDE, used in electronics casings and hard plastics; and Deca-BDE, with widespread applications (Alaee et al., 2003). PBDEs and PBBs are not covalently bound to products, and may be subject to migration from products. They are lipophilic, relatively persistent contaminants, and some congeners have been found to bioaccumulate and biomagnify in the food chain (Braekevelt et al., 2003; de Wit et al., 2010).

Several epidemiological studies provide indications that PBDEs may disrupt reproductive and thyroid hormone homeostasis in adult men (Meeker et al., 2009; Turyk et al., 2008), and there is growing evidence that prenatal or early-life exposure may impair neurodevelopment (Eskenazi et al., 2012; Herbstman et al., 2010). Smaller studies have also reported associations between serum PBDEs and decreased sperm motility and counts (Abdelouahab et al., 2011; Akutsu et al., 2008).

Commercial Penta- and Octa-BDE were banned in the EU in 2004, and soon after discontinued in the US (Cox and Efthymiou, 2003). Use of Deca-BDE will be restricted in the EU (ECHA, 2012) and phased out in the US in 2013 (US EPA, 2010). Despite restrictions and bans, human exposure to PBDEs and PBBs will continue as many products will not be replaced for years to come, these BFRs can be released during disposal, and they are persistent. Furthermore, production continues in other regions, and many BFRs undergo long-range transport (Bossi et al., 2008; Wania and Dugani, 2003).

Measurement of blood and breast milk PBDEs and PBBs levels have revealed large geographic differences in exposure levels (Frederiksen et al., 2009). Both food and household dust are important sources of exposure. There is some evidence that diet may be the predominant exposure pathway for Europeans (Fromme et al., 2009; Trudel et al., 2011), whereas it appears ingestion of dust contributes to a larger proportion of body burdens than food in the US, where flammability regulations are generally more stringent than in the EU (Harrad et al., 2010; Lorber, 2008; Schecter et al., 2006).

In this paper, we report the serum levels of BB-153 and PBDE congeners in men from Greenland, and two European cities: Warsaw, Poland and Kharkiv, Ukraine. We also examined potential determinants of exposure. Given that diet, lifestyle and housing factors differ among these three populations, we expected different exposure profiles. To our knowledge, this is the first description of blood BFR levels in these populations.

2. Materials and methods

2.1. Study design and populations

The study participants include male partners of pregnant women from Greenland, Poland and Ukraine. The study design and uniform data collection procedures have previously been described in detail (Jönsson et al., 2005; Toft et al., 2005). Briefly, couples were recruited for a time-to-pregnancy study during routine antenatal care visits between 2002 and 2004 from 4 settlements and 15 municipalities across Greenland, from a large central hospital in Warsaw, Poland, and from 3 maternity hospitals and 8 antenatal clinics in Kharkiv, Ukraine. Eligible participants were 18 years or older and born in the country. Of the 1710 couples enrolled (45% participation rate), male partners were consecutively invited to participate in a semen study until approximately 200 men at each site were enrolled. Participation rates were 79% in Greenland, 29% in Warsaw, and 33% in Kharkiv.

Participating men filled in a questionnaire on lifestyle factors including smoking and diet (seafood, alcohol and caffeinated beverage consumption) during the period "just before your wife/partner became pregnant", and on reproductive history and occupational exposures. Jobs were classified based on the International Standard Classification of Occupations (ISCO 88).

At the time of interviews, participants had blood samples drawn from a cubital vein into 10 ml vacuum tubes for serum collection without additives (Becton Dickinson, Meylan, France). Samples were immediately centrifuged and processed after clotting, and were shipped to Lund University for storage at −80 °C (Jönsson et al., 2005). Cotinine was analyzed in serum samples using liquid chromatography triple quadrupole linear ion trap mass spectrometry (Lindh et al., unpublished results).

BFRs were determined in a subset of 300 samples which had sufficient volume to perform these analyses, stratified by country, of the baseline 602. The mean age in the full cohort did not differ from the subset (29.84 years, SD ± 5.73 vs. 30.04 ± 5.88, p = 0.62). Among the included men, blood was collected between August 2002 and February 2004.

2.2. Determination of BFRs

Serum samples were analyzed for congeners BDE-28, 47, 99, 100, 153, 154 and 183 and BB-153 at the Norwegian Institute of Public Health in 2010–11. There were problems during preparation of one sample, leaving 299 serum samples for analysis. The PBDEs were extracted using automated solid-phase extraction according to the method described in (Thomsen et al., 2007). In brief, 2 g of serum was extracted using Oasis® HLB columns, and the extracts were subsequently cleaned up on sulfuric acid-silica columns with a layer of silica on top. The determination was performed by gas chromatography–high resolution mass spectrometry (GC–HRMS) using isotopically labeled (^{13}C) internal standards as previously described (Frederiksen et al., 2010).

BDE-183 (a major constituent of the Octa-BDE commercial mixture) was not detected in any sample. BDE-28 co-eluted with BDE-33 on the GC-column used. The reported concentrations for BDE-28 comprise the total of these two PBDEs. An unidentifiable interfering compound with the same mass fragments eluted closely after BDE-28/33. For samples from Greenland, this compound was present in larger amounts than BDE-28/33. Hence, BDE-28/33 could not be discerned from the interference and the concentrations presented (in the Supplemental material) comprise the total of these three compounds in the Greenlandic samples. The interference was present in much lower concentrations in samples from Ukraine, which made separate quantification of BDE-28/33 possible. The interference was rarely seen in samples from Poland.

Twenty-four aliquots of an in house quality control sample of human serum were analyzed alongside the 299 samples. The variation (RSD) of the determinations ranged from 6.6 to 11.4% for all PBDEs and was 13.7% for BB-153. The laboratory participated in the third round of the Arctic Monitoring and Assessment Programme (AMAP) Ring Test for Persistent Organic Pollutants in Human serum in 2010. All results were within ±31% of the consensus value. In addition, three samples from an AMAP ring test arranged previously were analyzed. These results were within ±21% of the consensus value.

All together 31 procedural blanks were analyzed. BDE-47 was detected in a large proportion of the blanks (>40%). No increasing or decreasing trend in the blank levels was observed throughout the study, so the median blank contamination level of 1.58 pg/g serum was subtracted from all individual measurements. The limits of quantification (LOQs) were set to the lowest determined concentrations with signal to noise ratios of ~3 (Supplemental material, Table S1). This corresponded approximately to the lowest level in the calibration curves, ranging from 0.02 to 0.12 ng/g lipids for the individual BFRs. LOQs were lower than those reported from several recent biomonitoring surveys which also used small aliquots of serum (Garí and Grimalt, 2013; Sjödin et al., 2008).

BFR concentrations were lipid adjusted (Braekevelt et al., 2003). Serum concentrations of triglycerides and cholesterol were determined by enzymatic methods (Jönsson et al., 2005). The total lipid concentration in serum (g/l) was calculated as total = 0.96 + 1.28 * (triglycerides + cholesterol) (Rylander et al., 2006), and median total lipids were 6.7, 6.5 and 4.6 g/l in Greenlandic, Polish and Ukrainian samples, respectively. Missing lipids data for 2 participants were imputed from a linear regression model of total lipids as a function of age, BMI and study population (R^2 = 0.32).

2.3. Statistical analysis

Concentrations of BFRs were natural log transformed because distributions were skewed. Data below the LOQ were imputed from a log-normal probability distribution via single conditional imputation, dependent on the study population and observed values for the other congeners and allowing the residual variances to vary by study population (Lubin et al., 2004). The lowest population-specific detected value (LOQ) was used for imputations (Supplemental material, Table S1). We summed the 5 tetra–hexa BDE congeners (Σ_5PBDE), converting wet weights to moles, and summing the products of moles and the weighted average molecular weight. Due to the observed interference in determination of BDE-28/33, we summed the congeners excluding this congener. These 5 congeners represent the most abundant constituents of the commercial Penta-BDE mixture (La Guardia et al., 2006). Summary statistics and exposure-determinant regression analyses were only computed for BFRs with detection frequencies (DF) of >70%; this cutoff leads to minimally biased parameter and variance estimates with the single imputation method we used (Lubin et al., 2004). Analyses of covariance (ANCOVA) were used to test for pairwise differences in age-adjusted BFR concentrations between study populations.

We fitted multiple linear regression models, including the following potential determinants of exposure: age (years), BMI (kg/m^2), serum cotinine levels (ng/ml), consumption of seafood (days/week), 'blue-collar' vs. 'white-collar' job title, and study population. Models included multiplicative interaction terms between each potential determinant and study population. For the Greenlandic study population, we also evaluated the impact of area of residence (mapped in Supplemental material, Fig. S1). As variance inflation factors were <1.4 for potential determinants in all models, multiple regression models were likely minimally biased by multicollinearity. We tested for non-linear associations with generalized additive models (GAMs) (Wood, 2011), and tested the sensitivity of models to deletion of extreme values. As a post-hoc analysis, we evaluated GAMs stratified by study population for age and PBDEs as we expected the emission scenarios for PBDEs to differ across the countries, and because others have reported non-linear relationships with age (Garí and Grimalt, 2013; Sjödin et al., 2008).

We examined Spearman correlations and performed a principal component analysis (PCA) of the BFRs with a DF of > 50% to evaluate patterns of clustering in the BFRs. For the PCA, data were mean-centered and scaled to unit variance. Finally, we examined the relative contribution of each BDE congener to the ΣPBDE. Statistical analyses were performed using R version 2.15.2 (R Core Team, 2012).

3. Results and discussion

3.1. Serum concentrations of BFRs

3.1.1. Current study

Characteristics of three study populations are presented in Table 1, and varied somewhat across populations. All men were between 18.5 and 49.7 years of age. The detection frequencies and concentrations of the analyzed BFRs and summed PBDE congeners are presented in Table 2. At least one BFR (PBDE or PBB) was detected in 298 of the 300 participants' serum samples, while all BFRs were detected in only 35 samples. BDE-47 and 153 were detected in more than 95% of samples in all three study populations. BDE-154 had the lowest DF—less than 37% across all three populations—and BDE-100 and BB-153 were detected in less than 20% of the Polish and Ukrainian samples. Concentrations of BFRs were significantly different between study populations (ANCOVA $p < 0.05$). Much higher concentrations of BFRs were observed in the samples from Greenland compared to the two European study populations for all analyzed BFRs. GM concentrations per congener were 2.7 to 15 times higher, and lipid adjusted GM Σ_5PBDE concentrations were a factor 3.5 to 7 times higher. The distributions of both lipid adjusted and wet weight concentrations are reported in the Supplemental material, Table S2. Wet weight GM Σ_5PBDE concentrations were 41.2 pg/g serum (95% CI 36.6, 46.9) in Greenlandic, 11.3 (9.5, 13.5) in Polish, and 4.2 (3.5, 4.9) in Ukrainian samples.

This study is the first large scale biomonitoring study of BFR levels in a Greenlandic, Polish or Ukrainian population. The study populations are representative of the general adult male populations, although no men above 60 years of age or infertile men were included. Somewhat lower concentrations might be expected in the female populations (Sjödin et al., 2008; Thomsen et al., 2007) due to differing exposure sources and elimination via lactation. The populations were sampled just prior to regulatory restrictions; however, exposure to the analyzed BFRs will continue due to their environmental persistence and the long lifetime of impregnated products.

A strength of this study is that blood was sampled from all three study populations according to a standardized protocol (Toft et al., 2005), and analysis of BFRs was conducted at one central laboratory. The concentrations observed in this study were comparable to those reported in two small studies (n < 50) which have reported associations between serum PBDEs and adverse effects on semen parameters (Abdelouahab et al., 2011; Akutsu et al., 2008), and a larger study (n = 405) which reported altered hormone levels in men (Turyk et al., 2008).

Future biomonitoring studies should also quantify other high-production volume flame retardants, such as organophosphorus flame

Table 1
Characteristics of the three male study populations.

	N	Greenland (n = 99)		Warsaw, Poland (n = 100)		Kharkiv, Ukraine (n = 100)		p-Value[a]
		Mean or %	±SD	Mean or %	±SD	Mean or %	±SD	
Age (years)	296	32.0	7.2	30.4	3.8	27.6	5.3	<0.0001
BMI (kg/m^2)	294	25.8	3.0	25.3	2.9	24.0	2.7	<0.0001
Current smoker[b]	299	60%		23%		68%		<0.0001
Smokers' cotinine (ng/ml)[c]	299	239.2	134.7	112.4	139.2	238.4	162.3	0.045
Seafood (days/week)	281	2.2	1.8	1.3	0.9	3.6	1.3	<0.0001
Area: North-West[e]	97	23%						
Mid-West[f]		48%						
South/East[g]		29%						
'White-collar' job title[d]	146	26%		90%		N/A	–	<0.0001

BMI, body mass index; N/A, not available; SD, standard deviation.
[a] Analysis of variance for means and chi-square test for proportions.
[b] Categorized as current smoker if serum cotinine exceeded 5.0 ng/ml (Benowitz et al., 2009).
[c] Median cotinine concentrations in smokers.
[d] ISCO-88 code was ≤52 (vs. reference ≥61 'blue-collar').
[e] Aasiaat, Ilulissat and Qeqertarsuaq (reference).
[f] Kangaamiut, Maniitsoq, Nuuk, Paamiut and Sisimiut.
[g] Imaarsivik, Kuummiut, Nanortalik, Narsaq, Qaqortoq and Tasiilaq.

Table 2
Lipid adjusted serum concentrations[a] (ng/g lipids) of BFRs in the three male study populations.

	Greenland (n = 99)				Warsaw, Poland (n = 100)				Kharkiv, Ukraine (n = 100)				ANCOVA p-value		
BFR	% DF	P50	P95	GM (95% CI)	% DF	P50	P95	GM (95% CI)	% DF	P50	P95	GM (95% CI)	GR vs. PL	GR vs. UA	PL vs. UA
BDE-47	98	2.0	6.9	1.8 (1.5, 2.1)	100	0.62	5.3	0.66 (0.50, 0.86)	99	0.24	1.1	0.12 (0.07, 0.20)	<0.0001	<0.0001	<0.0001
BDE-99	74	0.54	1.7	0.50 (0.43, 0.59)	23	<LOQ	1.7	–	56	0.22	0.66	–	–	–	–
BDE-100	73	0.55	1.6	0.43 (0.35, 0.51)	19	<LOQ	0.99	–	19	<LOQ	0.24	–	–	–	–
BDE-153	98	2.7	7.8	2.8 (2.5, 3.1)	98	0.52	1.6	0.58 (0.52, 0.65)	95	0.34	0.77	0.32 (0.29, 0.36)	<0.0001	<0.0001	<0.0001
BDE-154	36	0.06	0.54	–	17	<LOQ	0.23	–	22	<LOQ	0.14	–	–	–	–
Σ_5PBDE[b]	–	6.1	17.9	6.1 (5.4, 6.8)	–	1.32	10.3	1.7 (1.4, 2.0)	–	0.93	2.4	0.87 (0.75, 1.0)	<0.0001	<0.0001	<0.0001
BB-153	93	1.1	4.8	1.2 (0.9, 1.4)	16	<LOQ	0.32	–	2	<LOQ	0.22	–	–	–	–

ANCOVA, analysis of covariance; BB, bromobiphenyl; BDE, brominated diphenyl ether; BFR, brominated flame retardant; CI, confidence interval; DF, detection frequency; GM, geometric mean; GR, Greenland; PL, Poland; P50, 50th percentile; P95, 95th percentile; UA, Ukraine.
[a] Values < LOQ were imputed; GM is not presented if <70% DF or if interference.
[b] Sum of BDE-47, 99, 100, 153 and 154.

retardants (e.g., triphenyl phosphate), and novel or alternative brominated flame retardants (e.g., ethylene bis-tetrabromo phthalimide and 2,4,6-tribromophenol), some of which have been detected in the Arctic, indicating potential long-range transport (Covaci et al., 2011; De Wit et al., 2010).

3.1.2. Comparisons with reported concentrations

In Fig. 1, we compare levels of the most abundant BDEs (47 and 153) and $\Sigma_{tri-hepta}$PBDE observed in the current study with levels reported for other populations (n > 50 individual samples), not occupationally exposed or exposed to site-specific sources (e.g., living nearby an incinerator). The concentrations in Greenlandic men were higher than in European and Asian populations, but generally lower than those reported for North American populations. Relatively high PBDE concentrations in US populations (Frederiksen et al., 2009) have been attributed to more stringent furniture flammability standards. As with PBDEs, the level of serum BB-153 was higher in the US general population compared to BB-153 the Greenlandic population: GM of 2.8 ng/g lipids (95% CI 2.2, 3.5) in 988 US men (Sjödin et al., 2008) vs. 1.2 (0.9, 1.4) in 99 Greenlandic men.

In pooled plasma samples (n = 3–10) taken in 6 locations across the Russian Arctic, $\Sigma_{tri-hepta}$PBDE (28, 47, 99, 100, 153, 154 and 183) GM concentrations ranged from 0.12 to 0.93 ng/g lipids, with higher concentrations observed at the westernmost and easternmost areas — closer to European and North American source areas (AMAP, 2004). These concentrations are approximately one order of magnitude lower than those observed in the Greenlandic population.

Spatial trends in Arctic PBDE concentrations, as reviewed by de Wit et al. (2006, 2010), are also apparent in seabird eggs and marine mammals. Higher concentrations in East Greenland and Svalbard, compared to Russian and North American Arctic organisms, confirm that Western Europe and eastern North America are likely source areas. While long-range atmospheric transportation may be the primary source of BFRs in the Arctic environment, observations that air concentrations and ΣPBDEs in fish increase with proximity to highly populated settlements indicate that local sources also contribute (Christensen et al., 2002; de Wit et al., 2006). Open burning and municipal waste incineration are possible local sources.

Greenlanders have very high levels of some legacy persistent organic pollutants, such as PCBs, due to their high intake of contaminated fish and high trophic level mammals (i.e., seal, whale, polar bear) (Deutch et al., 2007). In a 2005–10 survey among 2742 Inuit from Greenland, traditional food accounted for 21% of energy intake and marine mammals for 12% (Jeppesen and Bjerregaard, 2012). In the current study populations, CB-153 was a factor 12 and 5 times higher in Greenlandic men compared to Polish and Ukrainian men, respectively (Jönsson et al.,

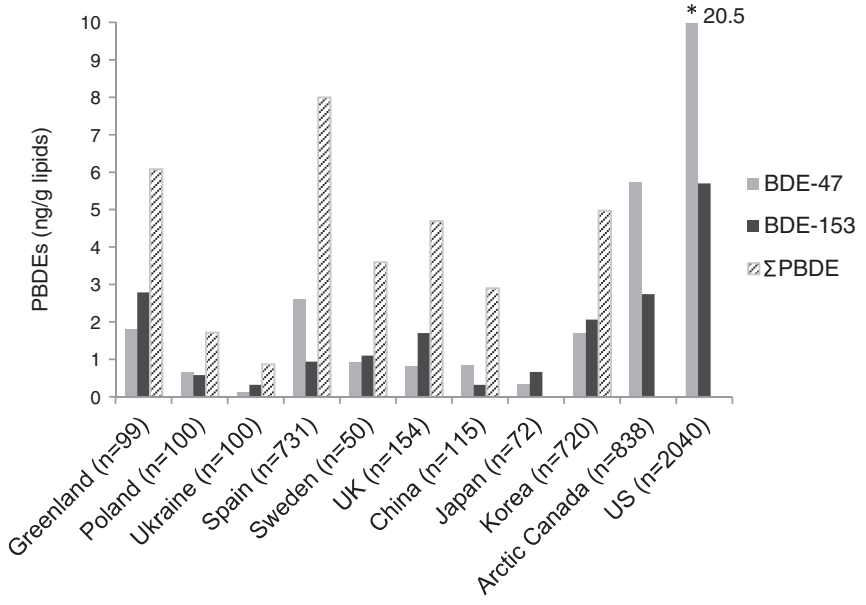

Fig. 1. Comparison of GM serum concentrations of BDE-47 and 153 and Σ_5PBDE among the men from Greenland, Poland and Ukraine (current study), with median or GM serum concentrations ($\Sigma_{tri-hepta}$PBDE) in general populations from Spain (Garí and Grimalt, 2013), Sweden (Weiss et al., 2006), the UK (Thomas et al., 2006), China (Zhu et al., 2009), Japan (Uemura et al., 2010), Korea (Kim et al., 2012), (plasma samples from Inuit from) Arctic Canada (Dallaire et al., 2009), and the US (Sjödin et al., 2008). European and North American populations were sampled sometime during the years 2000–04, and Asian populations during 2006–10.

2005). While PBDEs exhibit a somewhat lower biomagnification potential than PCBs in the Arctic marine food web (Hallanger et al., 2011; Kelly et al., 2008), diet is likely an important determinant of PBDE body burden for the Greenlandic population (Frederiksen et al., 2009). However, the relative importance of exposure via locally harvested food versus emissions from imported BFR-impregnated products and their disposal is unknown.

The concentrations in Polish and Ukrainian men of the current study were generally lower than in other populations, presumably because consumption of BFR-impregnated products was relatively low. Two studies assessed PBDE levels in samples of human breast milk from Polish women (Hernik et al., 2011; Jaraczewska et al., 2006), and levels were comparable yet at the low end of concentrations reported for other European countries (Frederiksen et al., 2009). In 2006–07, serum was sampled from 125 Slovak adults, two-thirds of whom lived in the vicinity of industry or an incinerator (Chovancová et al., 2012). Slovakia borders both Poland and Ukraine. Mean BDE-47 and 153 levels, 0.61 and 0.37 ng/g lipids respectively, lay between the levels observed in the Polish and Ukrainian populations, and the median $\Sigma_{\text{tri–hepta}}$PBDE of 0.86 ng/g lipids was lower.

3.2. Congener profiles

PBDEs with a DF of >50% were moderately correlated within the pooled study populations (r_s = 0.5–0.7), although some pairwise correlations were lower within specific populations, e.g., r_s = 0.2–0.3 between BDE-47 and 153 (Fig. 2 and Supplemental material, Table S3). BB-153 was moderately correlated with Σ_5PBDE (r_s = 0.4). For congeners with higher DFs, correlation patterns were generally consistent across study populations.

The PCA revealed differential clustering by study population, especially distinct for Greenland vs. the European populations: the scores for the three populations were located differently in the three-dimensional Euclidean space representing the first three principal components (Fig. 3). This clustering was not due to absolute differences in concentrations, as data were centered and scaled, nor was it an artifact of conditional imputation, as it was still evident in a PCA of only data > LOQ (Supplemental material, Fig. S2).

The relative contribution of congeners, by molar fraction, to Σ_5PBDE followed the same order in all three study populations: BDE-47 (40–58%) > 153 (19–40%) > 99 (9–23%) > 100 (7–9%) > 154 (1–3%). However, by weight, BDE-153 exceeded BDE-47 in the Polish population, and the ratio BDE-47:153 was higher in Polish compared to Greenlandic and Ukrainian samples. Examination of the congener distribution pattern across the continuum of ΣPBDE concentrations revealed that the ratio of BDE-47:153 relative concentrations increased with increasing ΣPBDE (Supplemental material, Fig. S3). Dallaire et al. (2009) also

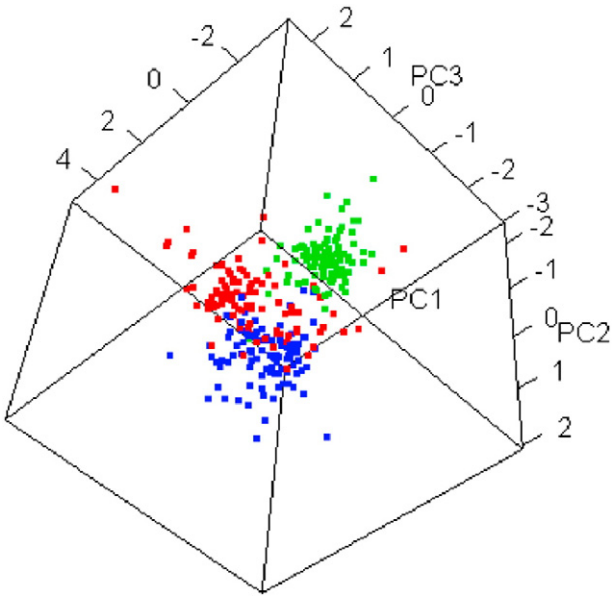

Fig. 3. Principal components analysis of BDE-47, 99 and 153, revealing clustering by population (green, Greenland; red, Poland; blue, Ukraine). Scores are projected onto the first three principal components, capturing 73%, 17% and 10% of the explained variance.

observed this pattern, and suggested that BDE-47 may represent more recent exposure and adoption of westernized lifestyle (diet and electronics use), whereas BDE-153 is a more persistent and ubiquitous congener.

BDE-47 or BDE-153 was also the dominant congeners in other large serum surveys in which BDE-209 was not measured (Sjödin et al., 2008; Thomas et al., 2006; Weiss et al., 2006). The relative contribution of congeners in serum did not match the (European Bromkal 70-5DE) Penta-BDE technical formulation, in which the order of most abundant congeners is BDE-99 (45% w/w) > 47 (43%) > 100 (8%) > 153 (5%) > 154 (3%) (La Guardia et al., 2006). This may be due to differing biomagnification and bioaccumulation potentials, and differing bioconversion and metabolic debromination rates across congeners (de Wit et al., 2010). Half-lives in humans have been estimated to be in the range of 1–3 years for BDE-47 and 99, and 6–7 years for BDE-153 (Geyer and Schramm, 2004; Trudel et al., 2011).

BDE-209, the major component of the Deca-BDE commercial mixture (>90%), was not quantified in the current study. BDE-209 has an estimated half-life of 15 days (Thuresson et al., 2006); much shorter than

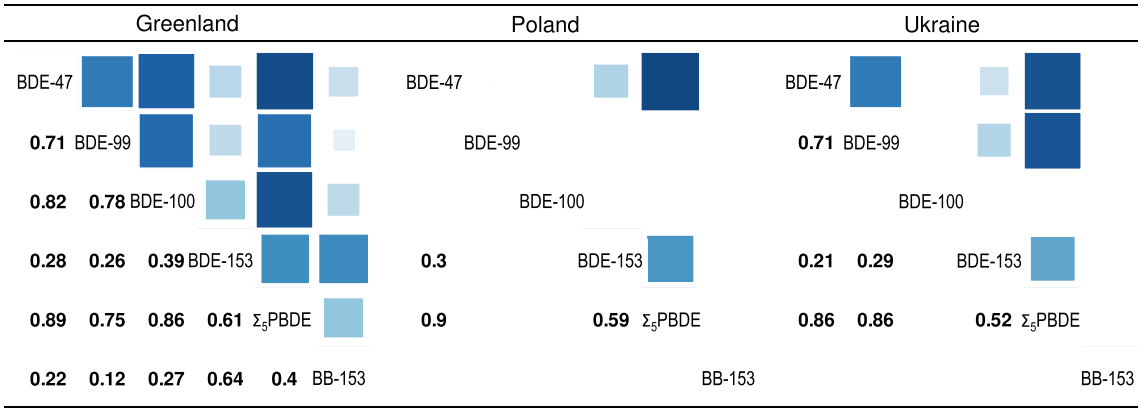

Fig. 2. Spearman correlation coefficients between BFRs with >50% DF within each population. Shading intensity and size of squares are proportional to the level of correlation.

the determined congeners. In a large survey of adults from Catalonia, Spain, BDE-209 was the most abundant congener in serum (the DFs for BDE-47, 153 and 209 were all above 70%). However, in other surveys, BDE-209 has been detected in a small proportion of serum samples (<35%) and was not the most abundant congener (Thomas et al., 2006; Vizcaino et al., 2011).

The distinct congener profiles per study population has implications for analyses of BFR exposure and health outcomes; different mixtures at various exposure ranges may produce different health effects across populations.

3.3. Regression analyses

Table 3 summarizes the linear regression models of PBDEs as a function of exposure determinants. Study population (Greenland) and area within Greenland were associated with BDE-153 and BDE-47, respectively, and with Σ_5PBDE. No other determinants were significantly associated with PBDEs. However, two interaction terms were significant (p-value < 0.05) and in regression models stratified by study population, seafood consumption was inversely associated with BDE-47, and age was positively associated with BDE-153 in Polish men, but not the other two study populations. BMI was borderline non-significantly associated with BDE-153 in all men; the coefficient was −0.038 (95% CI −0.078, 0.003), representing a change of 3.7% (95% CI −7.5, 0.0) per kg/m^2. We also evaluated multiple regression models of lipid weight BFRs and determinants, including total lipids as an independent variable. Results for these models were very similar to those presented in Table 3 (data not shown). Further, we tested linear regression models excluding 2 extreme values, and GAMs with all potential determinants included in the model. While no additional determinants were discovered, we did identify non-linear relationships for age (elaborated below).

Table 3
Multiple linear regression models of PBDEs (ng/g lipids) and potential exposure determinants.

Dependent variable, Potential determinant			Interaction p-value[a]	
	β	95% CI	GR	PL
Ln BDE-47: R^2 0.32				
1) Intercept	−2.983	−6.802, 0.837	–	–
Age (years)	−0.030	−0.099, 0.040	0.34	0.23
BMI (kg/m^2)	0.033	−0.103, 0.170	0.56	0.97
Cotinine (ng/ml)	0.001	−0.001, 0.003	0.25	0.41
Seafood (days/week)	0.178	−0.147, 0.503	0.25	**0.04**
Population[b]: GR	3.915	−1.362, 9.191	–	–
PL	0.864	−4.819, 6.547	–	–
2) White-collar job[c]	−0.140	−0.964, 0.684	–	0.55
3) Area[d]: South/East	**0.553**	**0.040, 1.066**	–	–
Mid-West	0.002	−0.457, 0.460	–	–
Ln BDE-153: R^2 0.77				
1) Intercept	−0.293	−1.434, 0.848	–	–
Age (years)	−0.002	−0.023, 0.019	0.81	**0.005**
BMI (kg/m^2)	−0.038	−0.078, 0.003	0.80	0.95
Cotinine (ng/ml)	0.0003	−0.0003, 0.001	0.79	0.12
Seafood (days/week)	0.009	−0.089, 0.106	0.86	0.62
Population: GR	**2.592**	**1.016, 4.168**	–	–
PL	−0.833	−2.531, 0.865	–	–
2) White-collar job	−0.118	−0.465, 0.228	–	0.90
3) Area: South/East	0.216	−0.107, 0.539	–	–
Mid-West	0.149	−0.140, 0.437	–	–
Ln Σ_5PBDE: R^2 0.55				
1) Intercept	−0.751	−2.401, 0.899	–	–
Age (years)	−0.011	−0.042, 0.019	0.43	0.11
BMI (kg/m^2)	0.025	−0.034, 0.083	0.19	0.62
Cotinine (ng/ml)	0.001	0.000, 0.002	0.30	0.13
Seafood (days/week)	0.059	−0.081, 0.200	0.27	0.26
Population: GR	**3.281**	**1.001, 5.560**	–	–
PL	0.293	−2.162, 2.748	–	–
2) White-collar job	−0.154	−0.675, 0.367	–	0.64
3) Area: South/East	**0.379**	**0.031, 0.727**	–	–
Mid-West	0.091	−0.219, 0.402	–	–

CI, confidence interval; GR, Greenland; (P)BDE, (poly)brominated diphenyl ether; PL, Poland.
Significant associations are marked in bold.
Model 1) included all determinants except job type and area (n = 275); Model 2) included all determinants except area, with a reduced complete case set (n = 130); Model 3) was fitted for the Greenland study population, and included all determinants except job type (n = 91).
R^2 reported for Model 1.
[a] P-values for the interaction terms between study population and determinant.
Reference categories:
[b] Ukraine;
[c] Blue-collar job;
[d] North-West.

3.3.1. Geographic differences

The majority of the variance was accounted for by only study population (R^2 of 0.30, 0.74 and 0.53 for BDE-47, 153 and Σ_5PBDE, respectively); exposure factors explained little additional variance (Table 3). Adding area of residence to the models for Greenland increased the R^2 from 0.03 to 0.11/0.09 for BDE-47 and Σ_5PBDE. Concentrations were higher in men from the South/East than in men from the North-West. GM Σ_5PBDE concentrations were 7.5, 5.6 and 5.3 ng/g lipids for those from the South/East, Mid-West and North-West, respectively. This East > West pattern was also mirrored in blubber samples from ringed seals, in which median BDE-47 concentrations were one order of magnitude higher in East vs. West Greenland samples (Rigét et al., 2006; Vorkamp et al., 2008). Greenlanders from the South/East consume more polar bear and Hooded seal—a large species of seal—which might partially explain the observed East > West difference in serum PBDE levels.

3.3.2. Age dependence

While linear regression models for age were null, we found associations of an increasing or U-shaped relationship between age and some PBDEs in GAMs stratified by study population. We present GAMs for age, plotted with BMI held at the mean level, as age and BMI were related (r_p = 0.15). BDE-47 showed a clear U-shaped relationship with age in Ukrainian men, with an inflection point around age 30 (Fig. 4). BDE-153 showed an exponential increase with age in Polish men. Upon deletion of two extreme values, this relationship became linear (presented). In Greenlandic men, the relationships were close to flat. The pattern for BDE-47 was paralleled by a U-shaped relationship between Σ_5PBDE and age in Ukrainian men.

Increasing concentrations of POPs, such as PCBs, with age has often been attributed to bioaccumulation with age. However, Quinn and Wania (2012) demonstrated that emissions-related cohort effects and the metabolic half-life are more important predictors of age-trends in body burdens, rather than bioaccumulation. Curvilinear relationships between age and PBDEs have also been observed in two other large general population surveys sampled in the same years as the currently studied populations (between 2002 and 2004). In 2040 men and women aged 12 and older from the US, BDE-47 and 153 showed a U-shaped relationship, with a inflection point (lowest concentrations) at 40–59 years (Sjödin et al., 2008). In 731 adults aged 18 to 74 from Catalonia, Spain, higher concentrations were observed in participants younger than 30 years for most congeners and ΣPBDE; ΣPBDE concentrations followed an L-shape (exponential decrease), and leveled off after 30 years (Garí and Grimalt, 2013). There were positive associations between age and lower-brominated (tri–hepta) but not higher-brominated (octa–deca) PBDEs in whole blood samples obtained in 2007–08 from 72 Japanese adults aged 15–74 (Uemura et al., 2010). Similarly, age was associated with the lower-brominated PBDEs in breast milk samples obtained in 2003–05 from 393 Norwegians aged 16–42 (Thomsen et al., 2010). Some studies of non-occupationally exposed populations (n > 50) sampled 2000–04 have found no relationship

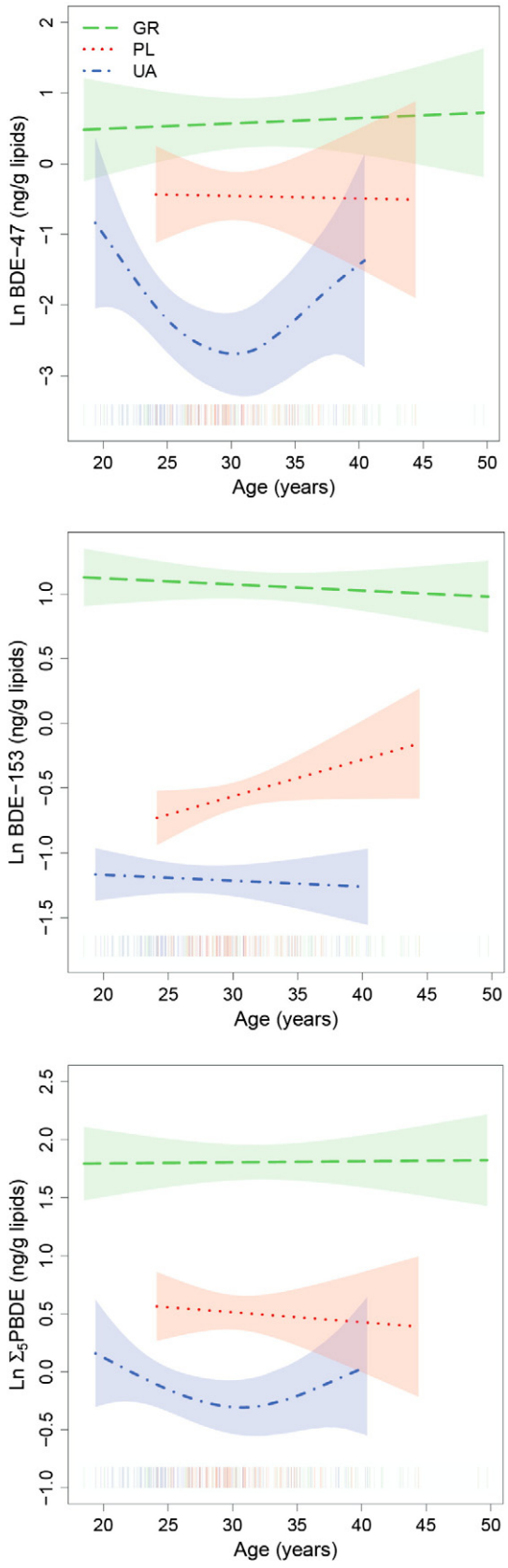

Fig. 4. Generalized additive models of age and PBDEs, modeled with BMI fixed at the mean. Population-specific splines and shaded 95% CIs are presented [green, Greenland (GR); red, Warsaw (PL); blue, Kharkiv (UA)]. Two extreme values were excluded to avoid a somewhat irregular curve.

between age and PBDE concentrations (Antignac et al., 2009; Thomas et al., 2006; Weiss et al., 2006).

BB-153 was phased out in the 1970s yet was detected in 93% of Greenlandic samples, and was positively and linearly associated with age (4.9%, 95% CI 2.2, 7.8%), seafood consumption (14.7%, 95% CI 3.4, 27.4%), and living in the South/East of Greenland (89.6%, 95% CI 11.2, 223.2%). BB-153 was detected in less than 20% of European samples (Table 2). In US adults sampled 2003–04, BB-153 also increased linearly with age (Sjödin et al., 2008).

3.3.3. BMI and other determinants

We found indications, although inconsistent and only borderline significant, that BDE-153 decreased with increasing BMI, possibly reflecting a dilution effect. This trend was also observed in the large surveys of Catalonians (non-significant) and Nunavik Inuit (for BDE-153 but not 47) (Dallaire et al., 2009; Garí and Grimalt, 2013). Seafood consumption was associated with decreased BDE-47 in the Polish population and non-significantly with Σ_5PBDE in all populations. In Nunavik Inuit, marine mammal intake and a biological marker of long-term seafood consumption, n-3 PUFA, was associated with decreased BDE-47, while store bought meat intake was associated with increased BDE-47 (Dallaire et al., 2009). In contrast, biological markers of fish consumption were associated with increased blood concentrations of lower (tri–hepta), but not higher, brominated BDEs in Japanese adults (Uemura et al., 2010). Biomagnification of tri–hepta BDEs has been observed in marine fish in the Baltic Sea and Greenland (Burreau et al., 2006; Christensen et al., 2002), and fish has been estimated to account for the majority of dietary PBDE intake (Frederiksen et al., 2009). While non-significant, we observed trends of increased PBDEs for smokers compared to non-smokers, and decreased PBDEs for those with a white-collar compared to blue-collar job. Higher PBDEs in smokers (Chovancová et al., 2012), in less educated (Thomsen et al., 2010) and those with lower household incomes (Zota et al., 2008) have been previously reported. Whether these variables are proxies for potentially more important determinants, such as composition of household products and diet, is unknown.

We had data on only a limited set of potential determinants of exposure, not including some exposure factors which have previously been associated with increased PBDE body burdens, such as living with an electrician (Thomsen et al., 2010), or owning a large screen TV (Buttke et al., 2013), or 3 or more pieces of stuffed furniture (Castorina et al., 2011). While this study does not provide new insights into the relative importance of household dust versus food as exposure pathways, the explained variance we modeled within populations (0.02–0.13) was in the range reported by other studies (0.04–0.28 (Buttke et al., 2013; Castorina et al., 2011; Dallaire et al., 2009; Thomsen et al., 2010)).

3.4. Conclusions

We report serum concentrations of tri- to hexa-BDEs and BB-153 in adult men from Greenland, Warsaw and Kharkiv. Body burdens were substantially higher in Greenlandic compared to European men, yet lower than concentrations reported for populations from the US. While we observed large contrasts in exposure and samples exhibited distinct population-specific congener profiles, data on potential determinants explained little variability. Future biomonitoring efforts should assess body burdens of novel BFRs, in addition to BFRs of the EU-restricted Penta-, Octa-, and Deca-BDE commercial mixtures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2013.09.001.

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