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Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men

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Abstract

Despite documented widespread human exposure to polybrominated diphenyl ethers (PBDEs) through dietary intake and contact or inhalation of indoor dust, along with growing laboratory evidence for altered endocrine function following exposure, human studies of PBDE exposure and endocrine effects remain limited. We conducted a preliminary study within an ongoing study on the impact of environmental exposures on male reproductive health. We measured serum hormone levels and PBDE concentrations (BDE 47, 99 and 100) in house dust from 24 men recruited through a US infertility clinic. BDE 47 and 99 were detected in 100% of dust samples, and BDE 100 was detected in 67% of dust samples, at concentrations similar to those reported in previous US studies. In multivariable regression models adjusted for age and BMI, there was a statistically significant inverse relationship between dust PBDE concentrations and free androgen index. Dust PBDE concentrations were also strongly and inversely associated with luteinizing hormone (LH) and follicle stimulating hormone (FSH), and positively associated with inhibin B and sex hormone binding globulin (SHBG). Finally, consistent with limited recent human studies of adults, PBDEs were positively associated with free T4. In conclusion, the present study provides compelling evidence of altered hormone levels in relation to PBDE exposures estimated as concentrations in house dust, and that house dust is an important source of human PBDE exposure, but more research is urgently needed.

Introduction

Polybrominated diphenyl ethers (PBDEs) are added to a variety of consumer products, including textiles, thermoplastics used in electronics (e.g. televisions, computers), and products containing polyurethane foam (e.g. mattresses, upholstered furniture), to make them difficult to burn. Additive flame retardants like PBDEs are not chemically bound (e.g. covalently bound) but are physically combined with polymers at levels ranging from 5 to 30% by weight, allowing PBDEs to leach out of the treated materials into the surrounding environment (ATSDR 2004). Thus, the presence of consumer products in the home that contain PBDEs can result in

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elevated PBDE concentrations in house dust (Allen et al. 2008a). Production of certain commercial PBDE formulations (PentaBDE and OctaBDE) has been banned in Europe and voluntarily discontinued in the US. However, the general population continues to be exposed to PBDEs due to their presence in home furnishings and persistence in the environment (EPA 2006).

Manufacture and use of PBDEs (primarily PentaBDE) has been much greater in North America than in Europe or other continents (ATSDR 2004). Accordingly, human biomonitoring studies of blood, breast milk, or adipose tissue samples have shown high geographic variability in exposure levels between continents, with PBDE concentrations among individuals in the US and/or Canada that are orders of magnitude higher than those found among European and other populations studied throughout the world (Schecter et al. 2005; ATSDR 2004; Sjodin et al. 2003). The primary routes of PBDE exposure to humans are likely ingestion of contaminated foods (primarily meat and dairy) and inhalation, ingestion and/or dermal uptake of house dust containing PBDEs released from electrical appliances and furniture (Lorber 2008; Allen et al. 2007; Webster et al. 2005; ATSDR 2004). In the US, recent evidence suggests PBDEs in the indoor environment may be a more important exposure source than diet, and exposure to PBDE in house dust likely accounts for the large differences in PBDE exposure between European and US populations (Frederiksen et al. 2008; Sjodin et al. 2008). One small US study found a stronger positive association between PBDE concentrations in breast milk and house dust PBDE levels (r=0.76) as compared to associations between PBDEs in breast milk and reported consumption of meat (r=0.37) and dairy (r=0.41) (Wu et al. 2007). Likewise, an EPA exposure assessment found that dietary intake alone could not explain US body burdens and estimated that 82% of the total PBDE intake was due to house dust (Lorber 2008).

PBDEs and hydroxylated PBDE metabolites are anti-androgenic *in vitro* by acting on, or interfering with, a number of potential targets within the hypothalamic-pituitary-gonadal axis (Stoker et al. 2005; Canton et al. 2008; 2007a; 2007b; 2006; Harju et al. 2007; He et al. 2008; Legler 2008). Experimental studies have also shown that PBDEs or their metabolites may impact thyroid function by altering thyroid hormone transport and metabolism/deactivation, by binding to thyroid hormone or other receptors, or through direct effects on thyroid gland tissue (reviewed by Darnerud 2008; Legler 2008). Because proper endocrine function is vital for human reproduction, development, and many other processes, there is growing concern for the potential endocrine effects associated with chemicals commonly encountered in the environment. Despite the documented widespread and escalating exposure to PBDEs among certain populations (e.g. North America) and concerns for endocrine disruption, there is a lack of human studies on the potential for adverse health effects in relation to exposure. Since PBDEs and other brominated flame retardants are prevalent in house dust and represent a primary source of exposure, we conducted an exploratory analysis to explore concentrations of PBDEs in house dust of participants in an ongoing study of male reproductive health and whether PBDEs were associated with hormone levels in the men.

Methods

Subject Recruitment

Men between 18 and 54 years of age were recruited from the Vincent Memorial Andrology lab at Massachusetts General Hospital (MGH) and invited to participate in a study to assess the effects of environmental exposures on male reproductive health. Participants included men from infertile couples due to a male factor, a female factor, or a combination of both. Approximately 65% of eligible men agreed to participate. Exclusionary criteria included prior vasectomy or current use of exogenous hormones.

Dust Sample Collection and Analysis

We collected used household vacuum bags from 24 non-smoking men between years 2002 and 2003. Existing vacuum bags were collected in the home by participants upon enrollment in the study, and were not selected for analysis of house dust PBDEs based on fertility status or projected exposure levels. Because the biologic half-lives of PBDEs vary by congener and can range from months to years (Birnbaum and Cohen Hubal 2006) the use of house dust as a marker of exposure may provide a reliable marker of long-term PBDE exposure. The use of vacuum bags from the homes of study participants is a validated cost-effective method of collecting household dust samples in epidemiological studies (Colt et al. 2008; 1998). Dust samples were sieved using a 150 μm screen to obtain the fine fraction, soxhlet extracted with 6% diethyl ether in hexanes, cleaned through a florisil column, and analyzed for PBDE congeners 47, 99 and 100 (three of the primary PentaBDE congeners) using GC/MS selected ion monitoring according to established protocols at Southwest Research Institute in San Antonio, TX (Rudel et al. 2003).

Serum hormones

One non-fasting blood sample from each of the 24 men was drawn and centrifuged, and the serum was stored at −80 °C until analysis. The hormone analytical methods have been previously described (Meeker et al. 2008). Briefly, testosterone was measured directly using the Coat-A-Count RIA kit (Diagnostics Products, Los Angeles, CA, USA), sex hormone binding globulin (SHBG) was measured using a fully automated chemiluminescent immunometric assay (Immulite: DPC, Inc., Los Angeles, CA, USA), and inhibin B was measured using a commercially available, double antibody, enzyme-linked immunosorbent assay (Oxford Bioinnovation, Oxford, UK). Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, prolactin, free T_4, total T_3, and thyrotropin (TSH) concentrations were determined by microparticle enzyme immunoassay using an automated Abbott AxSYM system (Abbott Laboratories, Chicago, IL, USA). The free androgen index (FAI) was calculated as the molar ratio of total testosterone to SHBG.

Statistical Analysis

Data analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). In preliminary analyses, Pearson correlation coefficients were calculated to assess bivariate relationships between PBDE concentrations in house dust and serum hormone levels. Multivariable linear regression was then used to assess these relationships while adjusting for potential confounding variables. Serum levels of several hormones (testosterone, inhibin B, estradiol, free T4 and total T3) closely approximated normality and were used in statistical models untransformed, while the distributions of several others (FSH, LH, SHBG, FAI, prolactin and TSH) were skewed right and transformed to the natural log (ln) for statistical analyses. PBDE concentrations in dust were also ln-transformed. All multivariable models were adjusted for age and BMI as continuous variables. The time of day and season in which the blood samples were collected from participants were also considered for inclusion in the models but did not act as confounders and were not retained in the final models. To improve interpretability, the regression coefficients were exponentiated and expressed as a percent change in the dependent variable (i.e., change in hormone levels relative to the study population median) for an interquartile range (IQR) increase in dust PBDE concentration.

Results

Table 1 presents the distribution of PBDE congeners 47, 99 and 100 measured in house dust. BDE 47 and 99 were detected in all 24 (100%) dust samples, while BDE 100 was detected in 16 (67%) samples. The three congeners were highly correlated (Spearman $r \geq 0.95$; correlations involving BDE 100 were ≥ 0.95 when setting non-detect values to one-half the limit of detection

[LOD] as well as when excluding non-detects), which suggests they may have originated from the same sources within the home. PBDE concentrations spanned three orders of magnitude and were highly skewed (log-normal distribution). Because the three congeners were highly correlated, values for samples with BDE 100 below LOD were then imputed using ln-transformed BDE 47 concentrations in a linear regression equation prior to further data analysis. The results for BDE 100 obtained using this method did not differ substantially from models utilizing other methods for assigning values below the LOD (random values below the LOD or assigning all samples a value equal to one-half the LOD).

Scatterplots of selected preliminary bivariate relationships are presented in Figures 1a through 1f. There was a suggestive negative correlation between PBDEs and FAI (Figure 1a), and statistically significant negative correlations between PBDE congeners and LH (Figure 1b) and FSH (Figure 1c). There were statistically significant positive correlations between PBDEs and inhibin B (Figure 1d) and free T4 (Figure 1e), and suggestive positive associations between PBDEs and estradiol (Figure 1f).

The multivariable linear regression results, presented as a percent change in hormone level associated with an interquartile range (IQR) increase in PBDE concentration adjusted for age and BMI, are reported in Table 2. Adjusted results were similar to the crude analysis with the following exceptions: When adjusted for age and BMI the inverse relationships between BDE 47 and 99 with FAI became statistically significant, a significant positive association between PBDEs and SHBG emerged, and the positive relationships between PBDEs and estradiol were no longer suggestive. IQR increases in BDE 47 and 99 were associated with a statistically significant 16% declines in FAI, and statistically non-significant 11% declines in testosterone. All three PBDE congeners were strongly and inversely associated with gonadotropin levels, where IQR increases in all three PBDE congeners were associated with decreases in FSH and LH of 30% or more. PBDEs were also positively associated with inhibin B and SHBG, where greater than 30% and 18% increases in hormone level, respectively, were found in relation to IQR increases in PBDEs. Finally, free T4 was positively associated with PBDE concentrations, but no associations were observed between PBDEs and total T3 or TSH. An IQR increase in house dust PBDE concentration was associated with a statistically significant 4% increase in serum free T4.

Discussion

In the present preliminary analysis involving only 24 men, we found statistically significant inverse associations between PBDEs in house dust and FAI, FSH and LH, and positive associations between PBDEs and inhibin B, SHBG, and free T4. The median and distribution of BDE 47, 99, and 100 in the present study were similar to those recently reported for dust from vacuum bags in US homes (Sjodin et al. 2008; Allen et al. 2008b). Thus, although our results should be interpreted with caution due to the small sample size, the possibility of altered hormone levels in relation to PBDE concentrations commonly encountered in the US may be of concern.

Human studies of PBDE exposure and endocrine function are limited. Consistent with our findings of an inverse association between PBDEs and FAI in the present study, a recent Dutch study of organohalogens and infant development reported a significant inverse relationship between BDE 99 measured in maternal serum and testosterone levels in male offspring at 3 months of age, while BDE 154 (a congener not measured in the present study) was positively associated with SHBG, inhibin B, and estradiol (Meijer et al. 2008). The authors also reported inverse associations between PBDE exposures and testis volume, further suggesting anti-androgenic effects. Animal studies provide support for anti-androgenic effects following PBDE exposure. Adult male rats exposed to a commercial PBDE mixture (PentaBDE)

experienced decreased epididymal, seminal vesicle and prostate weights, sperm head deformities, perturbations in circulating LH and testosterone levels, and altered activity of enzymes important for xenobiotic metabolism and steroidogenesis (van der Ven et al. 2008; Stoker et al. 2005). In male rats exposed *in utero*, BDE 99 exposure resulted in significant decreases in circulating sex steroids and anogenital distance at weaning that persisted into adulthood as well as alterations in the onset of puberty, decreased pituitary weights, and a feminization of sexually dimorphic behavior (Lilienthal et al. 2006). *In utero* exposure of rats to low levels of BDE 99 also resulted in significant and permanent reductions in spermatogenesis (Kuriyama et al. 2005), and male rats postnatally exposed to PentaBDE experienced delays in puberty and suppressed growth of androgen-dependent tissues (Stoker et al. 2005; 2004). However, since the majority of studies to date have investigated *in utero* or developmental exposure as opposed to exposure in adulthood, our ability to extrapolate from these studies to the present study is limited. Taken together, our results may imply that a reduction in FAI may be due to not only a subtle decline in testosterone, perhaps as a result of reduced LH, but also from an increase in SHBG, which could be secondary to increased free T4 and/or estradiol levels (Lo and Lamb 2004; Meikle 2004).

Inconsistent with our findings of an inverse association between PBDE exposure and LH, a recent Scandinavian study reported a positive association between the sum of 14 PBDE congeners measured in breast milk and serum LH among newborn males (Main et al. 2007). However, as mentioned above, it is difficult to directly compare effects in adults to those in newborns. The inconsistent findings between studies may be due to differences in study design (Main et al. was a case-control study of cryptorchidism), exposure measures (breast milk versus house dust) and/or exposure levels (US exposure levels are much higher than those measured by Main et al.), or may also reflect important differences in how PBDE exposure effects manifest as altered circulating hormone levels at different life stages. In addition to LH, the present study also found a significant inverse association between PBDEs and FSH and a positive association between PBDEs and inhibin B. While this is the first study to report these associations, the pattern of the relationships between PBDEs and hormone levels in men from these exploratory data may be suggestive of PBDE activity at the hypothalamus or pituitary of adult men, which may be consistent with recent toxicological data showing that the hypothalamus could be sensitive to BDE 47 and 99 uptake in the adult rat (Coburn et al. 2008), and that BDE 47 may affect hormone signaling pathways in the pituitary and brain of fathead minnows (Lema et al. 2008).

The positive relationship between PBDEs and free T4 in the present study is consistent with recent studies among adult males (Turyk et al. 2008; Bloom et al. 2008), but is inconsistent with animal studies of developmental exposure that have consistently reported PBDE exposure to be associated with declined T4 (Darnerud 2008; Legler 2008). These discrepancies potentially suggest that there could be important differences in PBDE effects on thyroid signaling and T4 levels when exposed developmentally as opposed to exposure in adulthood. In a recent study of 308 adult male sport fish consumers, Turyk et al. (2008) reported a positive association between the sum of four PBDE congeners (including 47, 99 and 100) and free T4 in serum, along with inverse associations between the sum of PBDEs and total T3 and TSH. Compared to the low tertile, the high BDE 99 tertile was associated with a statistically significant 8.4% increase in free T4 relative to the population median in multivariate regression models. The authors hypothesized that the increase in T4 may be related to PBDE inhibition of outer ring deiodinases involved in T4 conversion, or perhaps through a displacement of T4 from thyroid binding globulin by PBDEs or their metabolites. Bloom et al. (2008) also reported subtle and consistent, though not statistically significant, positive association between the sum of 9 PBDE congeners and free T4 in a small study of adult male anglers in New York. An earlier study of 110 adult males from Sweden and Latvia reported that plasma concentrations of BDE 47 were inversely and significantly associated with TSH, but not associated with total

T3 or T4 after adjusting for age (Hagmar et al. 2001). However, free T4 was not measured in the study. The present study is the first to assess house dust in relation to hormone levels, but the consistent finding of positive associations with free T4 between studies may support the utility of house dust PBDE concentrations as an estimate of exposure in epidemiologic investigations.

In conclusion, though some of the observed associations may be chance findings due to the number of comparisons made, we found compelling evidence of altered hormone levels in relation to PBDE concentrations in house dust. As this was only a preliminary study, these data need to be expanded to include additional PBDE congeners and other brominated flame retardant compounds on a larger sample. Further validation of the relationship between house dust PBDE concentrations and aggregate PBDE exposure is also needed. In addition, future animal and *in vitro* studies are also needed to elucidate biologic mechanisms, potential differences in endocrine effects at varying life stages, and the clinical and public health implications of hormone alterations associated with PBDE exposure.

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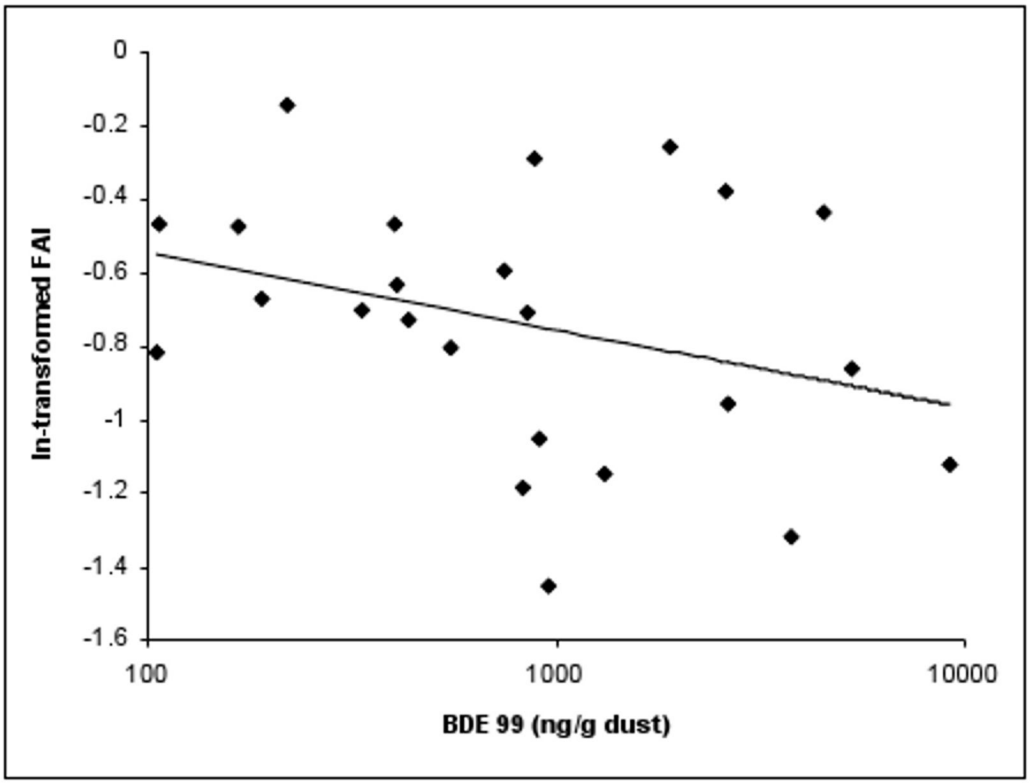
Figure 1a.



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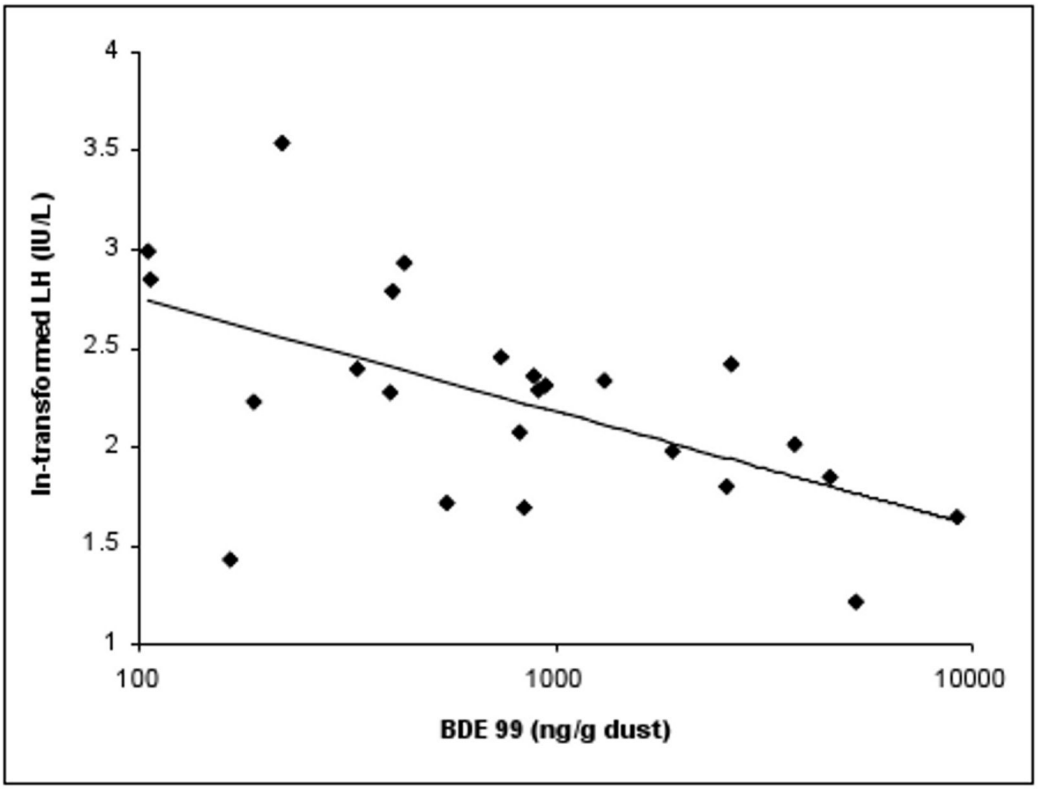

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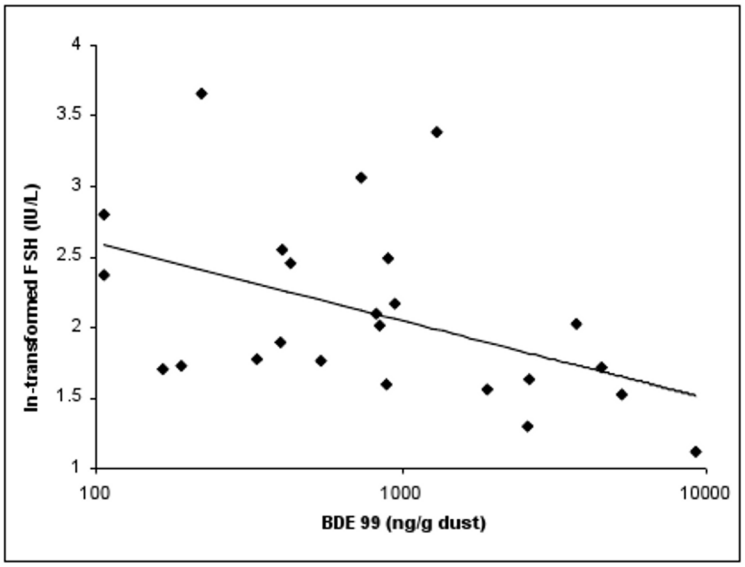

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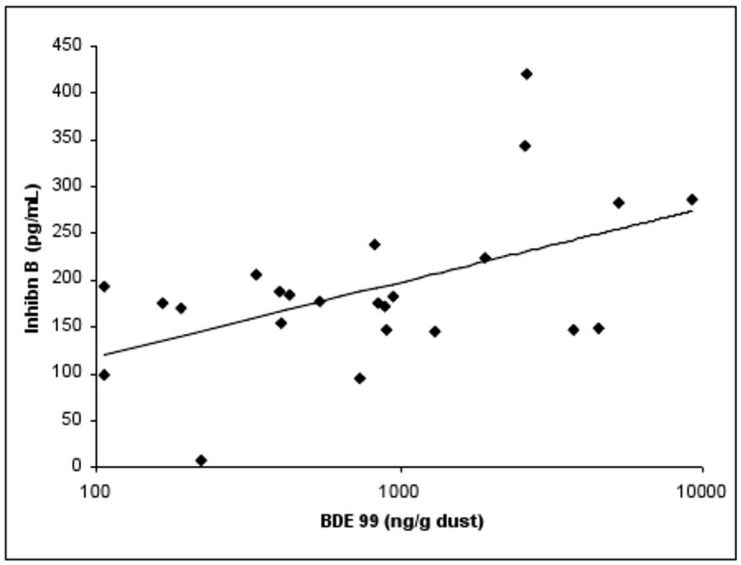

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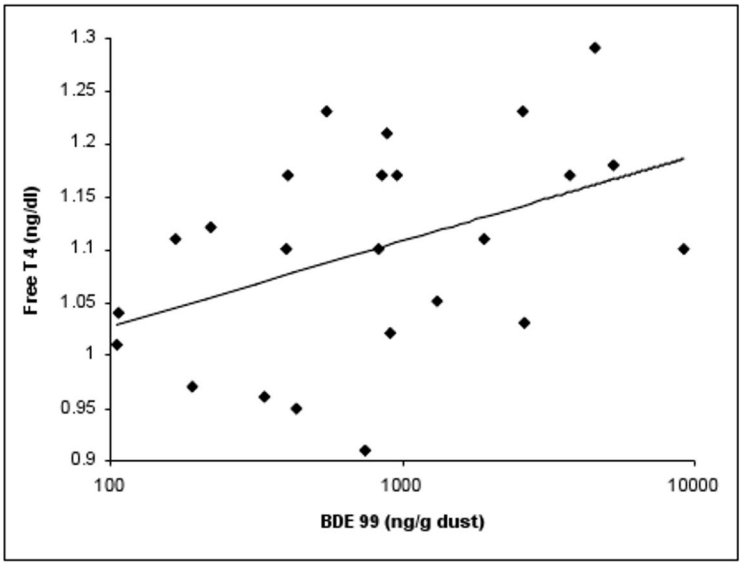

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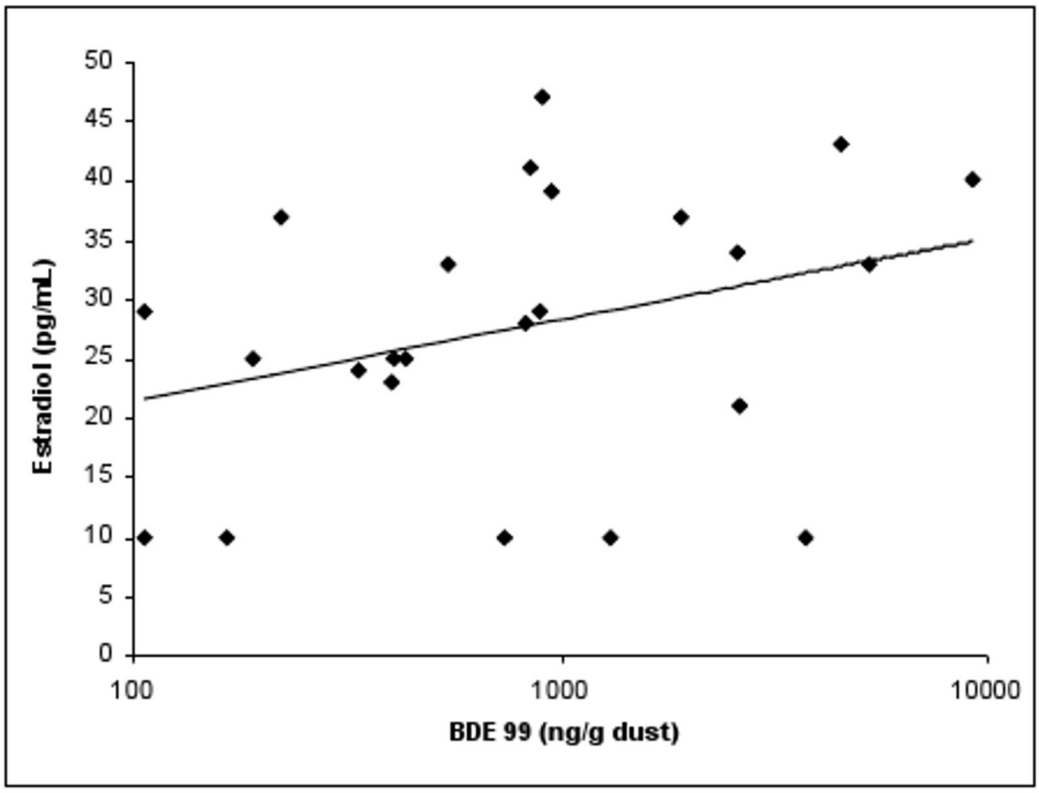

Figure 1.

Scatterplots of BDE 99 in house dust and serum hormone levels (N=24): **a)** free androgen index (FAI), r = -0.33 (p=0.12). **b)** LH, r = -0.57 (p=0.003). **c)** FSH, r = -0.46 (p=0.02). **d)** inhibin B, r = 0.51 (p=0.01). **e)** free T4, r = 0.44 (p=0.03). **f)** estradiol, r = 0.32 (p=0.12).

Table 1

Distribution of PBDE concentrations in house dust (ng/g of dust; n=24).

Congener	Geometric Mean	Selected Percentiles			
		25th	50th	75th	Maximum
BDE 47	577	302	500	1464	7620
BDE 99	809	370	838	2255	9220
BDE 100	220	ND	180	444	2830

ND = non-detect. The limit of detection was 83 ng/g for all 3 congeners.

Table 2

Adjusted[a] regression coefficients (95% confidence intervals) for percent change in hormone level (relative to population median) associated with an interquartile range increase in house dust PBDE concentration (N=24).

	BDE 47[b]	p-value	BDE 99[b]	p-value	BDE 100[b]	p-value
FSH[b]	-32.3% (-51.0, -6.3)	0.02	-32.6% (-51.6, -6.0)	0.02	-37.1% (-56.2, -9.6)	0.01
LH[b]	-30.9% (-45.6, -12.3)	0.004	-33.0% (-47.1, -15.3)	0.002	-33.3% (-49.4,-12.2)	0.006
Inhibin B	32.9% (10.7, 55.2)	0.006	32.7% (9.8, 55.7)	0.007	36.3% (10.7, 61.9)	0.008
Testosterone[c]	-11.0% (-29.2, 7.1)	0.22	-10.6% (-29, 7.9)	0.24	-9.2% (-30.5, 12.0)	0.37
SHBG[b]	18.8% (0.6, 40.2)	0.04	18.6% (-0.1, 40.6)	0.05	22.8% (1.6, 48.4)	0.03
FAI[b]	-16.4% (-29.2, -1.2)	0.04	-16.2% (-29.4, -0.5)	0.04	-16.5% (-31.2, 1.3)	0.07
Estradiol	8.9% (-12.0, 29.0)	0.38	13.2% (-7.5, 34.0)	0.20	13.3% (-10.0, 36.6)	0.24
Prolactin[b]	-4.6% (-22.3, 17.1)	0.63	-5.3% (-26.5, 19.8)	0.60	-6.0% (-27.3, 20.3)	0.61
Free T4	3.8% (0.2, 7.4)	0.04	4.1% (0.5, 7.8)	0.03	4.0% (-0.1, 8.2)	0.06
Total T3	-0.1% (-8.1, 8.1)	0.99	-0.2% (-8.5, 8.1)	0.96	0.8% (-8.3, 10.0)	0.85
TSH[b]	0.6% (-15.3, 19.0)	0.94	1.4% (-14.9, 20.9)	0.87	-2.5% (-19.8, 19.0)	0.78

[a] Adjusted for age and BMI.

[b] variable ln-transformed in statistical analysis

[c] Models for testosterone also adjusted for ln-transformed SHBG