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# Associations between brominated flame retardants in human milk and Thyroid-Stimulating Hormone (TSH) in neonates

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## Abstract

**Background—**Brominated flame retardants (BFRs) have been in widespread use in a vast array of consumer products since the 1970s. The metabolites of some BFRs show a structural similarity to thyroid hormones and experimental animal studies have confirmed that they may interfere with thyroid hormone homeostasis. A major concern has been whether intrauterine exposure to BFRs may disturb thyroid homeostasis since the fetal brain is particularly susceptible to alterations in thyroid hormones. However, few reports on newborns have been published to date.

**Objectives—**To evaluate the association between BFRs and neonatal thyroid-stimulating hormone (TSH).

**Methods—**We studied six polybrominated diphenyl ethers (PBDEs) measured in milk samples from 239 women who were part of the “Norwegian Human Milk Study” (HUMIS), 2003–2006. Hexabromocyclododecane (HBCD) and BDE-209 were measured in a subset of the women (193 and 46 milk samples, respectively). The milk was sampled at a median of 33 days after delivery. TSH was measured in babies three days after delivery as part of the routine national screening program for early detection of congenital hypothyroidism. Additional information was obtained through the Medical Birth Registry and questionnaires to the mothers.

**Results—**The PBDE concentrations in human milk in Norway were comparable to concentrations reported from other European countries and Asia, but not the US and Canada where levels are approximately one order of magnitude higher. We observed no statistically significant associations between BDE-47, 99, 153, 154, 209 and HBCD in human milk and TSH in models adjusted for possible confounders and other environmental toxicants including polychlorinated biphenyls (PCBs).



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**Conclusions—**We did not observe an association between TSH and exposure to HBCD and PBDEs within the exposure levels observed.

**Keywords**

brominated flame retardants; BDE-209; HBCD; thyroid-stimulating hormone; TSH; infants

## 1. Introduction

Brominated flame retardants (BFRs) are a group of chemical compounds which have been in widespread use since the 1970s, in a vast array of consumer products. Two of the three groups of BFRs which account for most of the world's production are hexabromocyclododecane (HBCD) and polybrominated diphenyl ethers (PBDEs). The recent ban in the US, Europe and Japan on the commercial PBDE mixtures Penta-BDE and Octa-BDE, as well as voluntary actions, has led to a decline in exposure to the congeners that were constituents (Fangstrom et al, 2008; Thomsen et al., 2010). The commercial mixture Deca-BDE (consisting mainly of BDE-209) has only been restricted in Europe so far, while HBCD is still in unrestricted use, and their use may increase as a result of the ban on other BFRs (Fangstrom et al, 2008; Hale et al., 2006). More knowledge of the potential health effects of exposure to BDE-209 and HBCD is therefore called for, although exposure to the Penta- and Octa-PBDEs mixtures will also continue for decades to come.

PBDEs share many toxicological properties with polychlorinated biphenyls (PCBs). A number of experimental animal studies have confirmed that PBDEs can interfere with thyroid hormone homeostasis (Darnerud, 2008). Among the many possible mechanisms for this interference, the evidence is strongest for effects mediated by changes in uridine diphosphate glucoronosyltransferase and by binding to transport protein (Darnerud, 2008; Richardson et al., 2008). During the pre- and postnatal period even slight disturbances in thyroid hormone homeostasis may cause long term effects on cognitive function, memory and hearing (Haddow et al., 1999; Morreale de et al., 2004; Porterfield, 1994). Subtle neurodevelopment effects were reported after exposure to relatively low doses of BFRs in experimental animal studies (Darnerud, 2008; Sand et al., 2004), including permanent effects on behavior, learning and memory that became more pronounced with increasing age (Eriksson et al., 2002; Viberg et al., 2003). These effects may have been mediated through thyroid disruption. It is worth noting that these effects were induced by exposure during neonatal brain development and not by exposure at later age stages, thereby indicating studies on newborns and children are needed.

To date, only two studies on the effect of PBDEs on thyroid function among neonates have been published. The results in one study suggest an association between exposure to PBDEs and a disruption in the levels of thyroid hormones (Herbstman et al., 2008b), whereas no association was observed in another study which included only nine subjects (Mazdai et al., 2003). However, concentrations of PBDEs may differ substantially across studies and give rise to different results.

In the present paper, we examined the association between BFRs in human milk and thyroid-stimulating hormone (TSH) as a measure of thyroid function. We studied six PBDEs in mother's milk from 239 mothers who were part of the "Norwegian Human Milk Study" (HUMIS). In addition, the levels of HBCD and BDE-209 were measured in a subset of 193 and 46 milk samples, respectively. We obtained TSH levels, measured in whole blood three days after delivery, from the nationwide neonatal screening program.

## 2. Materials and Methods

### 2.1 Study Population

HUMIS is a multi-center cohort of mothers who have recently given birth and their babies. The participants were recruited from six counties in Norway which covers northern, southern, inland and coastal areas of Norway. The majority of the participants were from five counties (Telemark, Oppland, Troms, Finmark and Rogaland), and within approximately two weeks of giving birth they were recruited by public health nurses who saw the subjects at home as part of a routine follow-up of all mothers in Norway. The participants from Oestfold county (n=50) were recruited in a slightly different manner by a pediatrician at the maternity wards from among mothers who had given birth to term babies. We asked all the mothers to save a 25 ml milk sample from each morning for eight consecutive days, although milk sampled otherwise was also accepted. The pooled samples were sent by regular mail, except in the county of Oestfold where they were collected by study personnel and kept frozen during transport. The median age at start of sampling was 33 days after delivery (min 2 days, max 124; $5^{th}$ percentile 16 and $95^{th}$ percentile 65). Further details are provided in the supplementary text and have previously been reported (Eggesbo et al., 2009). Information on gestational age, type of delivery and maternal thyroid disease was obtained from the Medical Birth Registry of Norway (MBR (Skjaerven et al., 2000)). Demographic information, the amount of breastfeeding each month and additional information were obtained from a questionnaire filled in by the mother after delivery (median 6 weeks later). Information on maternal smoking at the beginning of pregnancy was obtained from MBR (smoking during pregnancy).

HUMIS recruitment began in 2003 and is ongoing. Informed consent was obtained prior to the study and the study was approved by the Norwegian Data Inspectorate and Regional Ethics Committee for Medical Research. Overall, 36% of the invited women declined to participate in the study. As of November 2006, 2,146 mothers had agreed to participate in the HUMIS study, although 31% did not return any milk samples, partly due to lack of milk (Suppl. Figure A.1). Among the remaining 1,491 mothers, 350 were randomly selected, stratifying by county of residence. In addition, 46 samples were analyzed as part of a WHO human milk monitoring program (Colles et al., 2008). These 46 were randomly chosen from the HUMIS cohort among all the participants who met with the WHO criteria for inclusion: first-time mothers, being Norwegian, and having resided in Norway for the previous 5 years. In total, milk samples were analyzed from a total of 396 subjects. Of these 396 babies, 239 babies had accessible TSH values (see 2.2). The results of the chemical analysis, and the determinants for the levels of brominated flame in our Norwegian study have been published separately (Thomsen et al., 2010).

### 2.2 Outcome Variables

As part of the Norwegian Neonatal Screening Program, whole blood samples were obtained from all babies for the early detection of congenital hypothyroidism approximately 3 days after delivery and sent to the Neonatal Screening Unit at Oslo University Hospital, Rikshospitalet, Norway (median age 70 hours, mean 73, min 0, max 296, $5^{th}$ percentile 60, $95^{th}$ percentile 102 hours). The TSH level was measured in only two children prior to 48 hours after birth (one at the time of delivery and one at 45 hours), The TSH was measured on dried filter paper bloodspots by an immunoassay (AutoDelfia® neonatal TSH kits) (Perkin Elmer).

In February of 2004, the Neonatal Screening Unit began linking data for babies and their mothers to help facilitate the reporting of results. In our study sample, 239 babies were born after the said date. The analytical sensitivity of the assay is typically better than 2 mU/L, the

lowest point on the calibration curve is 1 mU/L and the between assay coefficient of variation is 9 at 14.6 mU/L, with values as low as 0.03 mU/L being reported. One subject had a value below this level and a result was not provided; in this instance a value of 0 was imputed.

### 2.3 Chemical Analysis

Concentrations of HBCD and eleven PBDE congeners (BDE-28, 37, 47, 85, 99, 100, 138, 153, 154, 183 and 209) were determined at the Department of Analytical Chemistry, Norwegian Institute of Public Health, according to a method described elsewhere in detail (Thomsen et al., 2010). BDE-209 was determined only in the 46 WHO samples. The extracts were analyzed by gas chromatography coupled to a mass spectrometer using electron capture negative ionization (GC-EC/MS) and an internal standard calibration as described by Thomsen et al (Thomsen et al., 2007). The HBCD isomers were not separated using GC, thus the total amount of HBCD was quantified. Concentrations of hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH), 1,1-dichloro-2,2-bis (p-chlorophenyl) ethene (*p,p′*-DDE), ten non dioxin-like polychlorinated biphenyls (PCB-28, 52, 74, 99, 101, 138, 153, 170, 180, and 194), and eight dioxin-like mono-*ortho* PCBs (PCB-105, 114, 118, 123, 156, 157, 167 and 189), were measured at the Norwegian School of Veterinary Science in Oslo in 15 ml aliquots of breast milk (Polder et al., 2009). All chemicals were expressed on a lipid basis for data analysis.

### 2.4 Data analysis

Linear regression was used to examine TSH as a continuous outcome in relation to potential confounders (Table 2) and in relation to BFRs (Table 3), while logistic regression was used to examine TSH dichotomized as either above the 80th percentile or not (Suppl. Table A.2). Linear regression was also used to determine mean lnTSH across categories of BFRs.

Due to a skewed distribution of TSH we used a natural log-transformation in all subsequent analyses. We divided subjects into six categories (sextiles) of exposure to BDE-47, 99, 153 and HBCD. We also calculated the sum of four congeners (BDE-28, 47, 99 and 100) and the sum of six congeners (BDE-28, 47, 99, 100, 153, 154) and divided these into sextiles. We chose sextiles a priori on an arbitrary basis due to the skewed distribution, since more categories would enable the detection of a threshold effect related to the highest exposure. Due to the smaller sample size for BDE-209, we divided subjects into two equally large categories of exposure. Finally, due to the large proportion of subjects with levels < LOQ for BDE-154 and HBCD, we divided subjects into five categories, choosing the highest imputed value as a cut-off value for the lowest category to ensure that all subjects with values < LOQ were in the reference category. Based on the categories, dummy variables were computed and used in the analysis.

We then examined the natural log of TSH in relation to categories of BFR and in relation to BFR level as a continuous variable. In the adjusted analysis, the linear regression models included a priori the following covariates: age at which TSH was measured (continuously in hours), county of residence, and pre-pregnancy maternal body mass index. We also considered the following potential confounders: maternal education as a socioeconomic index (less than 12, 12, 13 to 16 and >16 years of education), Norwegian nationality, season, parity, smoking, maternal age at delivery, sex, pregnancy hypertension and/or preeclampsia based on maternal reports (yes/no) and type of delivery (spontaneous, induced, assisted, or cesarean); and as continuous variables: gestational age, HCB, β-HCH, *p,p′*-DDE, oxychlordane, and the sum of all PCB congeners (PCB-28, 52, 74, 99, 101, 105, 114, 118, 138, 153, 156, 157, 167, 170, 180, 189, 194). The covariates were categorized as in Table 2

unless otherwise noted above. Missing values for "age at which TSH was measured" were replaced by mean values (n=80).

Confounding was evaluated by using a SAS ® macro, starting with a model with all a priori and potential confounders included, that enabled an automated backward elimination of covariates whose deletion resulted in minimal changes in the coefficient for the exposure variable. Potential confounders to be included in the final model were identified using the following criterion: relative to the overall mean lnTSH, excluding the variable from the model caused the adjusted coefficient (comparing the highest and lowest exposure categories) to change by more than 5%. A similar approach was also implemented with the BFRs represented as continuous variables.

The results of both analyses were used to determine whether the covariate was a confounder and for the sake of consistency, all covariates selected as a confounder for one compound were included in the final models for all compounds. Once the final set of covariates was identified, we also fit adjusted logistic models, with TSH dichotomized.

We then grouped PCBs congeners together in several different ways to convey different modes of action for a potential confounding mechanism and repeated the final models including either: a) sum of 6 PCBs (PCB-28, 52, 101, 138, 153, 180), b) sum of PCBs that are suspected enzyme inducers (PCB-52, 99, 101, 118, 153, 156, 157, 167, 180, 189, 194) (Chevrier et al., 2007), c) sum of dioxin-like mono-*ortho* PCBs (PCB-28, 74, 105, 114, 118, 156, 157, 167, 189) and finally d) sum of di-*ortho* PCBs (PCB-52, 99, 101, 138, 153, 180, 194).

Furthermore, we repeated the analysis by: 1) Restricting the analysis to subjects who had information on age when TSH was measured, and who had it measured at least 45 hours after delivery (all but one), 2) Repeating the analysis excluding WHO participants and 3) Repeating the analysis including the duration of breastfeeding prior to milk sampling (see supplementary text for detailed description of how this covariate was calculated).

Modification of the association between BFRs and TSH was evaluated for sex, PCBs, maternal smoking, and type of delivery by using cross-product terms in the models. If the p-value for effect modification was <0.1 then stratified results were examined. For this purpose type of delivery was categorized as either a "spontaneous, unassisted vaginal delivery" (n=153), or an "induced, assisted or C-section delivery" (n=84, with 43 cesarean sections) in order to replicate the analysis of a previous study (Herbstman et al., 2008b).

## 3. Results

### 3.1 Study Population and Levels

The study population was similar to both the general population of recent mothers in Norway and to all participants recruited to the HUMIS study with the exception of smoking, which was less frequent in the present study sample (Suppl. Table A.1). There were no participants diagnosed with congenital hypothyroidism.

The mean concentration of TSH was 1.4 mU/L (median 1.1 mU/L), ranging from 0.0 mU/L to 17.3 mU/L, and the difference between the $10^{th}$ and the $90^{th}$ percentiles was 2.4 mU/L. The median TSH level according to characteristics of the participants is shown in Table 2. TSH was related to age at screening in a crude analysis. However, in an adjusted analysis, including all factors listed in Table 2, no significant association was observed between TSH and any factor (Table 2).

The percentages of non-detects, levels and range of the studied BFRs are shown in Table 1. Data on the correlation among each BFR and the determinants of these, including geographical differences across counties, have previously been reported (Thomsen et al., 2010).

### 3.2 Association between Each of the Chosen Flame Retardants and TSH

We observed no statistically significant associations between TSH and any BFR, whether the BFRs were entered continuously or in categories (Table 3). Repeating the fully adjusted analyses with TSH as a dichotomous outcome, no statistically significant consistent trends were observed, again whether BFRs were entered continuously or in categories (Suppl. Table A.2). Substituting the sum of all measured PCBs with the sum of six indicator PCBs, the sum of enzyme inducing PCBs or with PCBs grouped into di-*ortho* and mono-*ortho* congeners, did not alter the results, nor did adjusting for breastfeeding prior to milk sampling.

When we restricted the analysis to a) the random sample excluding the WHO sample and b) subjects in whom we had information on age when TSH was measured and had it measured at least 45 hours after delivery, no statistically significant associations were observed.

No apparent effect modification of the BFR-TSH association was seen after stratifying by sex (interaction terms all above $p > 0.17$), by PCBs (interaction terms all above $p > 0.2$), by current or past smoking (interaction terms all above $p > 0.19$), or by type of delivery ($p > 0.19$).

## 4. Discussion

The present study did not find any associations between the levels of BFR measured in human milk and TSH levels in newborns. Our results do not exclude the possibility that exposure to higher levels of BFRs, such as those reported in North America or at the higher end of our population exposure distribution, may affect thyroid homeostasis. Furthermore, our study size, especially for BDE-209, was small.

Our study is limited by the retrospective assessment of exposure since human milk was sampled approximately one month after TSH was measured. Although a retrospective assessment of exposure is generally not raised as a major concern in studies on persistent organic pollutants due to their long half lives, variation in feeding patterns as well as toxicokinetics may introduce a differential change in concentrations. On the other hand, recent studies indicate that while variable, the average monthly decrease in milk PBDEs is only 2–3% (Daniels et al., 2010; Hooper et al., 2007). In accordance with this, no significant association between the duration of breastfeeding and the sum of the six PBDEs was observed in our data: the crude association between the amount of previous breastfeeding and the sum of six PBDEs was: beta; 0.013 (CI −0.04 to 0.06), p- value: 0.62. (See Suppl. Text A). Finally, the sensitivity analysis performed with adjustment for total breastfeeding before the sampling date revealed no changes in the results.

Milk levels are being used as a proxy for maternal blood levels in this study. A high correlation between PBDEs in milk and maternal serum has been reported (BDE-153; $r = 0.85$ for maternal serum-milk) (Cariou, 2006; Guvenius et al., 2003), as has a similar correlation between milk and cord blood (BDE-153; 0.84 for cord-milk) (Cariou, 2006). For lower brominated congeners, the correlation may be even higher (BDE-47; $r = 0.94$, $p < 0.01$, for cord blood-human milk) (Guvenius et al., 2003), which may be explained by their lower mass which probably enables easier transport through the placental barrier (Guvenius et al., 2003). Thus, the levels of higher brominated congeners in human milk may

overestimate prenatal exposure. However, milk levels may still appropriately rank subjects according to their exposure levels unless the placenta barrier functions differently among women.

The PBDE exposure levels observed in the present study are comparable to concentrations in human milk from most other Asian and European countries, except for the UK and the Faroe Islands where slightly higher levels were reported and for the US and Canada where levels are approximately one order of magnitude higher (reviewed in (Frederiksen et al., 2008). The HBCD and BDE-209 levels observed in the present study are also comparable to the levels reported in Europe, except somewhat higher levels of BDE-209 have been reported in Spain (Covaci et al., 2006; Frederiksen et al., 2008).

Human studies on this topic are still scarce. Studies among adults have reported an association between exposure to BFRs and subtle differences in thyroid hormones among sport fishermen, workers occupationally exposed to BFRs, Inuit adults and subfertile men (Dallaire et al., 2009; Hagmar et al., 2001; Julander et al., 2005; Meeker et al., 2009; Turyk et al., 2008), while others report no effects among sport fishermen (Bloom et al., 2008). Among pregnant women an inverse association between TSH levels and concentrations of BFRs in serum was observed (Chevrier et al., 2010). Finally, two studies report that prenatal exposure to BFRs is associated with neurodevelopmental findings in young children (Herbstman et al., 2010; Roze et al., 2009). Concentrations of PBDEs may differ substantially across studies from different countries and give rise to different results.

Of greater relevance to the current study is a study in which three PBDEs were examined in relation to thyroid function in infants (Herbstman et al., 2008b). BDE-100 and BDE-153 were weakly associated with increased odds of having a cord blood total T4 in the lower quintile. Furthermore, BDE-47 was associated with reduced odds of having a cord serum TSH level in the upper 20th percentile. Compared to the latter study, our levels are 5–15 times lower, which could explain the discrepant finding. No association was observed between total and free T4 thyroid hormone levels and the sum of six PBDEs in a study from Indianapolis which, however, only included 9 babies (Mazdai et al., 2003).

A limitation in our study is the lack of measurement of thyroxin. However, TSH is regarded as a sensitive marker of thyroid disruption in humans since incremental changes in free T4 hormone concentrations will lead to logarithmic changes in TSH (Bursell et al., 2007). TSH has also been extensively evaluated as a marker of thyroid disruption in newborns due to its frequent use in screening programs. On the other hand, a number of experimental animal studies on BFRs failed to detect any association with TSH (Hallgren et al., 2001) in the presence of an association with thyroxin. The mechanism by which BFRs could affect thyroxin but not TSH remains unclear. Nevertheless, some animal studies do report an effect on TSH by BFRs (Stoker et al., 2004; van der Ven et al., 2006). In conclusion, we cannot exclude the possibility that thyroid homeostasis was disrupted in ways that are not reflected in altered TSH levels.

We did not have data on iodine status but due to fortification of cattle fodder iodine deficiency is rare in Norway (Delange, 1994), and none of the subjects in the present study had a clinically elevated TSH.

To the best of our knowledge, this is the first study in which milk was sampled over a prolonged period of time (eight days). This was done in order to reduce the within-subject variability in milk that has been demonstrated for other persistent organic pollutants (Skaare et al., 1990; Thomsen et al., 2010).

One strength of this study is that TSH was measured at a median of 70 hours after birth, thereby allowing for the birth-related temporary spike in TSH and hormone levels to abate. TSH in newborns has been reported to be associated with a number of factors; however, this is mainly in relation to TSH levels measured in cord blood (Herbstman et al., 2008a). Studies of TSH measured 24 hours or longer after birth generally report no associations between TSH and factors such as preeclampsia (Belet et al., 2003), preterm delivery (Carrascosa et al., 2004) or mode of delivery (Turan et al., 2007). Furthermore, studies with repeated measurements have shown that preterm delivery is significantly associated with TSH only within the first 24 hours after birth and not after 24 hours, although this may not hold true for very preterm babies (Biswas et al., 2002; Murphy et al., 2004). This indicates that these factors are related to the TSH-surge after birth and not to the thyroid function per se. In our study, only two infants had their TSH measured earlier than 48 hours after delivery, which probably accounts for why no covariates showed any association with TSH.

An advantage of the present study was the availability of data on coexisting environmental contaminants. Since environmental contaminants coexist in exposure sources and may have additive or antagonistic effects, this may be important. Still, adjustment for other contaminants can only be partially achieved, and we cannot exclude the possibility of confounding by other as yet unmeasured persistent organic pollutants that are strongly correlated with BFR exposure in Norway.

One weakness of our study is the low final response rate. Hence, the results may not be generalizable to the entire population. However, a comparison between our study sample and the general population of recent mothers did not reveal any strong selection with regard to the covariates available for comparison (Suppl. Table A.1). A differential selection that is related to both exposure to brominated flame retardants and to TSH levels is possible though seems unlikely.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The study was approved by the Regional Ethics Committee for Medical Research in Norway (ref. S-02122) and the Norwegian Data Inspectorate (refs 2002/1398-2 and 02/01398-7), and participation did not occur until after informed consent was obtained.

## Abbreviations

| | |
|---|---|
| **BFR** | Brominated flame retardant |
| **BMI** | Maternal body mass index |
| **DDE** | 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethene |
| **HBCD** | Hexabromocyclododecane |
| **HCB** | Hexachlorobenzene |

| | |
|---|---|
| **HCH** | Hexachlorocyclohexane |
| **HUMIS** | The Norwegian Human Milk Study |
| **MBR** | Medical Birth Registry |
| **PCBs** | Polychlorinated biphenyls |
| **PBDEs** | Polybrominated diphenyl ethers |
| **POPs** | Persistent Organic Pollutants |
| **T4** | Thyroxine |
| **TSH** | Thyroid-stimulating hormone |

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Highlights

- Exposure to brominated flame retardants may disturb thyroid homeostasis.
- We examined the association between eight BFRs in human milk and thyroid-stimulating hormone (TSH) measured three days after delivery.
- We did not observe an association between TSH and exposure to HBCD and PBDEs.

**Table 1**

Concentrations of selected BFRs in ng/g lipids in human milk samples.

| | n | % >LOQ | mean[a] | min[a] | 25 perc | median | 75 perc | Max |
|---|---|---|---|---|---|---|---|---|
| BDE-47 | 239 | 100 | 1.7 | 0.15 | 0.64 | 0.95 | 1.60 | 56 |
| BDE-99 | 239 | 100 | 0.44 | 0.02 | 0.16 | 0.26 | 0.39 | 9.5 |
| BDE-153 | 239 | 99.6 | 0.56 | 0.01 | 0.29 | 0.42 | 0.64 | 5.0 |
| BDE-154 | 239 | 71.6 | 0.05 | 0.01 | 0.01 | 0.03 | 0.05 | 1.2 |
| BDE-209[b] | 46 | 76.1 | 0.50 | 0.005 | 0.12 | 0.25 | 0.47 | 5.8 |
| HBCD[c] | 193 | 67.9 | 1.10 | 0.10 | 0.10 | 0.54 | 0.98 | 31 |

[a] For values of BFRs <LOQ, LOQs/$\sqrt{2}$ were imputed and used in the calculations, see Thomsen et al., 2010. The mean lipid concentration in the milk samples was 3.6% (median 3.5%).

## Table 2

Median TSH levels in blood (mU/L), taken postnatal day three, in 239 babies, according to characteristics of the mother and the baby.

| | n=239 (%) | TSH median | Crude p-value* | Adjusted p-value** |
|---|---|---|---|---|
| All | | 1.08 | | |
| Sex | | | *0.86* | *0.19* |
| Female | 45.6 | 1.06 | | |
| Male | 54.4 | 1.11 | | |
| Nationality | | | *0.97* | *0.91* |
| Norwegian | 88.6 | 1.10 | | |
| Not Norwegian | 11.4 | 1.04 | | |
| Parity | | | *0.18* | *0.81* |
| No previous children | 49.4 | 1.01 | | |
| One or more | 50.6 | 1.20 | | |
| Gestational age (weeks) | | | *0.41* | *0.18* |
| <37 | 4.6 | 0.80 | | |
| 37–42 | 92.5 | 1.10 | | |
| >42 | 2.9 | 0.86 | | |
| Birth weight (g) | | | *0.51* | *0.80* |
| <2500 | 2.1 | 1.43 | | |
| ≥2500 | 97.9 | 1.08 | | |
| Birth season | | | *0.55* | |
| Winter | 33.1 | 1.09 | | *ref* |
| Spring | 24.7 | 1.01 | | *0.43* |
| Summer | 21.3 | 0.94 | | *0.46* |
| Fall | 20.9 | 1.24 | | *0.84* |
| Maternal age (years) | | | *0.89* | *0.35* |
| <28 | 41.8 | 1.09 | | |
| 28 to 31 | 30.1 | 1.07 | | |
| >31 | 28 | 1.07 | | |
| Maternal smoking *a* | | | *0.08* | *0.33* |
| None | 88 | 1.13 | | |
| Any | 12 | 0.94 | | |
| Maternal BMI ($kg/m^2$) *b* | | | *0.30* | |
| <18.5 | 3.9 | 0.72 | | *ref* |
| 18.5–24.9 | 59.8 | 1.06 | | *0.57* |
| ≥25 | 36.3 | 1.15 | | *0.72* |
| Age at screening (hours) | | | *0.01* | *0.42* |
| <48 | 0.8 | 1.00 | | |
| 48–71 | 39.3 | 1.26 | | |
| ≥72 | 26.4 | 0.89 | | |
| Missing information | 33.5 | 1.04 | | |

| | n=239 (%) | TSH median | Crude p-value* | Adjusted p-value** |
|---|---|---|---|---|
| Type of delivery | | | *0.46* | *0.52* |
| Spontaneous | 64.6 | 1.06 | | |
| Assisted or C-section | 35.4 | 1.09 | | |
| County of residence | | | *0.78* | |
| Ostfold | 14.2 | 1.04 | | *0.93* |
| Oppland | 28.5 | 1.09 | | *0.81* |
| Telemark | 15.1 | 1.19 | | *ref* |
| Rogaland | 18.4 | 1.18 | | *0.12* |
| Tromso | 17.2 | 1.01 | | *0.95* |
| Finmark | 6.7 | 1.30 | | *0.64* |

[a] Maternal smoking at the beginning of pregnancy

[b] Maternal pre-pregnancy body mass index (BMI)

* P-value based on Kruskal Wallis.

** P-value from linear regression model, in which all the covariates listed in the Table were entered. For covariates entered as dummies, reference category is shown, otherwise covariates were entered continuously.

**Table 3**

Crude and adjusted associations between prenatal exposure to BFRs as measured in human milk, and neonatal TSH levels. Logtransformed values are given for TSH

| | | | | Crude model | | | | Adjusted model [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **BFRs (ng/g lipid)** | | **N** | **lnTSH** | | **(95%** | **CI)** | **lnTSH** | | **(95%** | **CI)** |
| | | | **Mean** | **b** | **lower** | **upper** | **Mean** | **b** | **lower** | **upper** |
| All | | 239 | 0.8 | | | | | | | |
| BDE-47 | | | | | | | | | | |
| | 0.15 – 0.51 | 39 | 0.78 | | | | 0.75 | | | |
| | 0.52 – 0.750 | 40 | 0.84 | 0.06 | −0.12 | 0.25 | 0.81 | 0.06 | −0.14 | 0.26 |
| | 0.751 – 0.95 | 40 | 0.73 | −0.05 | −0.23 | 0.14 | 0.68 | −0.07 | −0.26 | 0.13 |
| | 0.953 – 1.29 | 40 | 0.76 | −0.02 | −0.21 | 0.16 | 0.70 | −0.05 | −0.26 | 0.15 |
| | 1.32 – 1.86 | 40 | 0.83 | 0.05 | −0.14 | 0.23 | 0.75 | 0.00 | −0.20 | 0.20 |
| | 1.87 – 55.76 | 40 | 0.81 | 0.03 | −0.16 | 0.21 | 0.75 | 0.00 | −0.21 | 0.20 |
| | Per IQR units[b] | 239 | 0.80 | 0.00 | −0.01 | 0.01 | 0.80 | −0.00 | −0.01 | 0.01 |
| BDE-99 | | | | | | | | | | |
| | 0.021 – 0.132 | 39 | 0.73 | | | | 0.67 | | | |
| | 0.133 – 0.192 | 40 | 0.87 | 0.14 | −0.05 | 0.32 | 0.80 | 0.13 | −0.07 | 0.34 |
| | 0.194 – 0.257 | 40 | 0.81 | 0.08 | −0.10 | 0.27 | 0.77 | 0.10 | −0.10 | 0.29 |
| | 0.258 – 0.322 | 40 | 0.74 | 0.01 | −0.17 | 0.20 | 0.67 | 0.00 | −0.20 | 0.20 |
| | 0.325 – 0.493 | 40 | 0.74 | 0.01 | −0.17 | 0.20 | 0.65 | −0.02 | −0.22 | 0.18 |
| | 0.504 – 9.518 | 40 | 0.87 | 0.14 | −0.05 | 0.32 | 0.81 | 0.14 | −0.06 | 0.35 |
| | Per IQR units[b] | 239 | 0.80 | 0.00 | −0.01 | 0.02 | 0.80 | 0.00 | −0.02 | 0.02 |
| BDE-153 | | | | | | | | | | |
| | 0.019 – 0.256 | 39 | 0.82 | | | | 0.75 | | | |
| | 0.257 – 0.334 | 40 | 0.76 | −0.06 | −0.24 | 0.13 | 0.70 | −0.05 | −0.24 | 0.15 |
| | 0.337 – 0.412 | 40 | 0.73 | −0.08 | −0.27 | 0.10 | 0.66 | −0.08 | −0.28 | 0.12 |
| | 0.415 – 0.551 | 40 | 0.88 | 0.07 | −0.12 | 0.25 | 0.79 | 0.04 | −0.15 | 0.24 |
| | 0.555 – 0.747 | 40 | 0.79 | −0.02 | −0.21 | 0.16 | 0.71 | −0.03 | −0.23 | 0.16 |

| | | | | Crude model | | | | Adjusted model [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **BFRs (ng/g lipid)** | **N** | **lnTSH** | | **(95% CI)** | | **lnTSH** | | **(95% CI)** | | |
| | | **Mean** | **b** | **lower** | **upper** | **Mean** | **b** | **lower** | **upper** |
| | 0.754 – 4.960 | 40 | 0.80 | −0.02 | −0.20 | 0.17 | 0.68 | −0.07 | −0.27 | 0.14 |
| | Per IQR units[b] | 239 | 0.80 | 0.02 | −0.01 | 0.06 | 0.80 | 0.03 | −0.02 | 0.07 |
| BDE-154 | | | | | | | | | | |
| | 0.011 – 0.012 | 69 | 0.77 | | | | | | | |
| | 0.013 – 0.024 | 38 | 0.76 | −0.01 | −0.18 | 0.15 | 0.72 | −0.04 | −0.21 | 0.14 |
| | 0.025–0.034 | 43 | 0.76 | −0.01 | −0.17 | 0.15 | 0.68 | −0.03 | −0.20 | 0.14 |
| | 0.035–0.05 | 44 | 0.84 | 0.07 | −0.09 | 0.22 | 0.69 | 0.07 | −0.10 | 0.25 |
| | 0.051–1.18 | 45 | 0.86 | 0.09 | −0.06 | 0.25 | 0.79 | 0.06 | −0.11 | 0.24 |
| | Per IQR units[b] | 239 | 0.80 | 0.00 | −0.01 | 0.21 | 0.78 | 0.00 | −0.02 | 0.22 |
| BDE-209 | | | | | | | | | | |
| | 0.005 – 0.248 | 23 | 0.78 | | | | 0.50 | | | |
| | 0.250 – 5.800 | 23 | 0.76 | −0.01 | −0.28 | 0.26 | 0.60 | 0.10 | −0.24 | 0.45 |
| | Per IQR units[b] | 46 | 0.80 | 0.00 | −0.04 | 0.05 | 0.80 | −0.02 | −0.10 | 0.06 |
| Sum4PBDEs[c] | | | | | | | | | | |
| | 0.26 – 0.86 | 39 | 0.83 | | | | 0.73 | | | |
| | 0.87 – 1.26 | 40 | 0.80 | 0.00 | −0.19 | 0.18 | 0.73 | 0.00 | −0.20 | 0.21 |
| | 1.27 – 1.558 | 40 | 0.78 | −0.02 | −0.20 | 0.17 | 0.73 | 0.00 | −0.20 | 0.20 |
| | 1.560 – 2.01 | 40 | 0.72 | −0.08 | −0.27 | 0.11 | 0.62 | −0.12 | −0.32 | 0.09 |
| | 2.05 – 2.92 | 40 | 0.85 | 0.05 | −0.14 | 0.23 | 0.76 | 0.03 | −0.17 | 0.23 |
| | 2.96 – 78.53 | 40 | 0.80 | 0.00 | −0.18 | 0.19 | 0.69 | −0.04 | −0.25 | 0.16 |
| | Per IQR units[b] | 239 | 0.80 | 0.00 | −0.01 | 0.01 | 0.80 | −0.00 | −0.01 | 0.01 |
| Sum6PBDEs[d] | | | | | | | | | | |
| | 0.52 – 1.18 | 39 | 0.78 | | | | 0.71 | | | |
| | 1.20 – 1.72 | 40 | 0.85 | 0.07 | −0.11 | 0.26 | 0.78 | 0.07 | −0.13 | 0.28 |
| | 1.73 – 2.07 | 40 | 0.75 | −0.03 | −0.22 | 0.15 | 0.68 | −0.03 | −0.23 | 0.18 |
| | 2.074 – 2.64 | 40 | 0.74 | −0.04 | −0.22 | 0.15 | 0.67 | −0.03 | −0.23 | 0.17 |

| | | | | Crude model | | | | Adjusted model [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **BFRs (ng/g lipid)** | | **N** | **lnTSH** | | **(95%** | **CI)** | **lnTSH** | | **(95%** | **CI)** |
| | | | **Mean** | **b** | **lower** | **upper** | **Mean** | **b** | **lower** | **upper** |
| | 2.65 – 3.56 | 40 | 0.78 | 0.00 | −0.18 | 0.19 | 0.66 | −0.04 | −0.24 | 0.15 |
| | 3.6 – 81.6 | 40 | 0.87 | 0.10 | −0.09 | 0.28 | 0.78 | 0.08 | −0.13 | 0.29 |
| | Per IQR units[b] | 239 | 0.80 | 0.00 | −0.01 | 0.02 | 0.80 | 0.00 | −0.01 | 0.01 |
| HBCD | | | | | | | | | | |
| | 0.1 | 62 | 0.76 | | | | 0.65 | | | |
| | 0.13 –0.52 | 31 | 0.76 | 0.00 | −0.19 | 0.19 | 0.64 | −0.01 | −0.21 | 0.20 |
| | 0.53–0.79 | 33 | 0.77 | 0.01 | −0.17 | 0.19 | 0.67 | 0.02 | −0.18 | 0.22 |
| | 0.8 –1.24 | 33 | 0.87 | 0.11 | −0.08 | 0.29 | 0.78 | 0.12 | −0.08 | 0.33 |
| | 1.29–31.2 | 34 | 0.80 | 0.04 | −0.14 | 0.22 | 0.68 | 0.03 | −0.17 | 0.23 |
| | Per IQR units[b] | 193 | 0.80 | −0.00 | −0.02 | 0.02 | 0.80 | −0.00 | −0.02 | 0.02 |

[a] Adjusted for age at TSH screening test, maternal BMI, county, ppDDE, HCB and delivery type (spontaneous, induced, assisted, or caesarean) and pregnancy preeclampsi or hypertension. None of the covariates were significantly associated with TSH. Sample mean was imputed for children with missing information for age at screening test; n=80. Missing information maternal BMI; n=5, delivery type; n=2 and preeclampsi/hypertension; n=1, leaving 230 subjects for the adjusted analysis.

[b] Model in which the compound was entered continuous and the betas are given for a change in units corresponding to the interquartile range of exposure for the compound in question.

[c] Sum of four congeners: BDE-28, 47, 99 and 100.

[d] Sum of six congeners: BDE-28, 47, 99, 100, 153, 154.