Health consequences of exposure to brominated flame retardants: A systematic review

Young Ran Kim, Fiona A. Harden, Leisa-Maree L. Toms, Rosana E. Norman

The University of Queensland, School of Population Health, Herston, QLD 4006, Australia
Queensland University of Technology, School of Clinical Sciences and Institute of Health and Biomedical Innovation, George St., Brisbane, QLD 4000, Australia
The University of Queensland, Queensland Children's Medical Research Institute, Herston, QLD 4029, Australia

HIGHLIGHTS

- Systematic review conducted to find a relationship between BFR and human health.
- 36 epidemiological studies were included and analysed.
- We found suggestive evidence that exposure to BFR is harmful to health.
- Causal relationships between BFR exposure and human health are hard to establish.

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ABSTRACT

Background: Brominated flame retardants (BFRs), are chemicals widely used in consumer products including electronics, vehicles, plastics and textiles to reduce flammability. Experimental animal studies have confirmed that these compounds may interfere with thyroid hormone homeostasis and neurodevelopment but to date health effects in humans have not been systematically examined.

Objectives: To conduct a systematic review of studies on the health impacts of exposure to BFRs in humans, with a particular focus on children.

Methods: A systematic review was conducted using the MEDLINE and EMBASE electronic databases up to 1 February 2012. Published cohort, cross-sectional, and case-control studies exploring the relationship between BFR exposure and various health outcomes were included.

Results: In total, 36 epidemiological studies meeting the pre-determined inclusion criteria were included. Plausible outcomes associated with BFR exposure include diabetes, neurobehavioral and developmental disorders, cancer, reproductive health effects and alteration in thyroid function. Evidence for a causal relationship between exposure to BFRs and health outcomes was evaluated within the Bradford Hill framework.

Conclusion: Although there is suggestive evidence that exposure to BFRs is harmful to health, further epidemiological investigations particularly among children, and long-term monitoring and surveillance of chemical impacts on humans are required to confirm these relationships.

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1. Introduction

Brominated flame retardants (BFRs) are commonly used in electronics, clothes, toys, motor vehicles, plastics, and textiles to reduce flammability (Chen et al., 2009; Dirtu and Covaci, 2010). This group of chemicals consists of tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs), polybrominated biphenyls (PBBs), and hexabromocyclododecane (HBCD) (Diru and Covaci, 2010). Three commercial PBDE formulations have been produced: penta-BDE, octa-BDE and deca-BDE (US Department of Health and Human Services, 2004). The penta-BDE product was used mainly in flexible polyurethane foam for mattresses and cushioning, octa-BDE in the plastics industry in computer casings and monitors and deca-BDE in high impact polystyrenes and other materials for electronic and electrical appliances, the automotive industry, construction and building applications as well as textiles (US Department of Health and Human Services, 2004). These compounds are lipophilic and persistent and can concentrate in animal fats and fish species. The harmful health effects of these chemicals can be related to their persistency, bioaccumulation and biomagnification potential in humans (Eljarrat et al., 2004). BFRs are increasingly present in the environment and humans. The major routes of exposure are dietary sources, inhalation and ingestion through dust in indoor environments and occupational exposure (Birnbaum and Staskal, 2004).

Despite cessation of penta- and octa-BDE manufacture in many developed countries, concentrations in humans have increased (Schecter et al., 2005). In Australia, BFRs have been in use since the 1970s but importation of penta- and octa-BDE products ceased in 2005 (NICNAS, 2007). Nevertheless, concentrations in humans are reported to be higher than those found in Europe and Asia but lower than in North America with the congener, PBDE-47 being the most prominent in human blood in Australia and overseas (Thomsen et al., 2002; Schecter et al., 2005; Toms et al., 2009). In particular, concentrations of PBDEs are highly elevated in Australian children at four to five times that of adults (Toms et al., 2008). Other studies have also reported higher concentrations of BFRs in paediatric versus adult serum (Fischer et al., 2006; Sjödin et al., 2008; Toms et al., 2009) and can most likely be attributed to breastfeeding and dust ingestion from mouthing behaviours and playing closer to ground level. Thus the dynamic physiology of children combined with the way they interact with their environment results in higher exposures than adults in the same environment (Landrigan et al., 2004). In addition, young children have decreased metabolic capacity to detoxify and eliminate environmental contaminants (Landrigan et al., 2004). Furthermore, the continuing growth and maturation of their immune and neurological systems make them especially vulnerable to the adverse effects of environmental exposures (Landrigan et al., 2004). The potential health consequences of this increased paediatric body burden remain largely unknown and require further investigation (Landrigan et al., 2004; Stapleton et al., 2005, 2008; Toms et al., 2008), particularly in light of increasing evidence that many adult diseases may originate during foetal development and early childhood.

A number of experimental animal studies have explored and identified the association between BFR exposure and adverse health effects (Blake, 2011; Chhabra et al., 1993; Canton et al., 2008; Imai et al., 2009; He et al., 2011a). Kim et al. (2009) reported that exposure of pregnant rats to PBDE-209 was linked to increased thyroid stimulating hormone (TSH) levels in their offspring. In rats, thyroxine (T₄) and triiodothyronine (T₃) were decreased in the study population when exposed to 0.3 mg/kg or more of PBB (Gupta et al., 1983). Reduced plasma T₄ levels in male rats 10 and 20 days after exposure to PBB with subsequent disruption of normal homeostasis of the pituitary thyroid axis and PBB accumulation in the thyroid have also been observed (Allen-Rounds et al., 1981). In rats, exposure to commercial mixtures of BFRs have been associated with: alterations in thyroid hormone homeostasis; developmental neurotoxicity and neurobehavioural changes as well as reproductive health effects, including a delay in puberty and a decrease in ventral prostate and seminal vesicle weights at the high dose in male rats (Birnbaum and Staskal, 2004) leading to concerns over the potential impact on human health.

Studies reviewing the current data on BFRs exploring the main sources, distribution, exposure pathways, and toxicity, as well as the potential health risks of exposure have been published (Legler and Brouwer, 2003; Sjödin et al., 2003; Birnbaum and Staskal, 2004; Dasso et al., 2010; Kefeni et al., 2011). Legler and Brouwer (2003) have identified BFRs as a possible endocrine disrupting...
chemical (EDC). Early life exposure to EDCs may lead to endocrine disorders or diseases particularly in children and during fetal development (Legler and Brouwer, 2003; Sjödin et al. 2003) and Daso et al. (2010) reviewed literature based on human exposure to PBDEs, including human exposure routes and levels. According to Sjödin et al. (2003), food intake was the main route of human exposure for adults and breast milk for young children. The majority of studies have reported the most dominant PBDE congener in human tissues to be PBDE-47 (e.g. Sjödin et al., 2003; Daso et al., 2010). The aim of the current study was to conduct a systematic review of the scientific literature to summarise the evidence relating to the possible relationship between exposure to BFRs and health outcomes in humans.

2. Method

The review was carried out using general recommendations from The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) revision, which is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses, with reference to processing and reporting of results (Moher et al., 2009). The PRISMA checklist (see Supporting Information Text S1) was used as a guideline to report this systematic review.

2.1. Inclusion and exclusion criteria

This systematic review incorporated retrospective and prospective cohort studies, cross-sectional and case-control studies meeting the following inclusion criteria: (1) reported original, empirical research published in a peer reviewed journal, (2) considered exposure to BFRs as a potential risk factor for loss of health, and (3) considered health outcomes for which standardised diagnostic criteria are available. The included studies reported effect size estimates and confidence intervals. Relevant articles included epidemiological studies exploring BFR exposure, with specific health outcomes, such as reproductive health, neurobehavioral and developmental disorders, cancer, diabetes and alterations in thyroid hormone levels.

2.2. Search strategy description

The electronic databases MEDLINE and EMBASE were searched for studies published up to 1st February 2012. The search strategy was developed in consultation with a librarian and the following keywords were included: exposure; brominated flame retardants; tetrabromobiphenol A; polybrominated diphenyl ethers; and hexabromocyclododecane. The health consequences of exposure to BFRs in humans and specific diseases were not specified in the search ensuring that it was kept broad and inclusive (see Supporting Information Text S2). The search was not restricted to the English language, nor restricted by any other means. Articles in languages other than English were translated.

2.3. Data collection

The full-text article of any study that appeared to meet the inclusion criteria was retrieved for closer examination. Two reviewers (YRK and LT) independently assessed articles for eligibility. Disagreements were resolved by consensus (YRK, LT, FH and RN). A standardised data extraction form was developed and data retrieved included: publication details (year of publication); country where study was conducted; methodological characteristics such as sample size and study design, exposure and outcome measures, type of BFR and chemical analysis, age, whether blood or breast milk samples were used, health outcome assessment and effect size with 95% confidence intervals. The coders were not masked to the journals or authors of the studies reviewed.

3. Results

3.1. Study selection

In total, 1502 potentially relevant journal articles were identified from the database search, and 5 additional studies were identified from reference lists. A total of 1005 articles were screened after duplicates were removed. A further 913 records were then excluded mainly because they were animal or human cell line studies. Of 92 full-text articles assessed for eligibility, 36 met the inclusion criteria and reported effect size and uncertainty information (Fig. 1).

3.2. Study characteristics

Among the 36 selected articles, there were 22 cohort studies, six cross-sectional studies and seven case-control studies. All but one study were published between 2000 and 2011. The majority of included studies (n = 31) were from the United States of America (USA) with two Swedish, one Taiwanese (Chao et al., 2010), one Spanish (Gascon et al., 2011) and one Norwegian (Eggesbo et al., 2011) study included. Although the majority of articles were conducted on PBDEs (n = 20), and PBBS (n = 16), one study also examined HBCD (Eggesbo et al., 2011). Seventeen child-related studies were extracted, and the studies explored the association between paediatric health and BFR exposure through a child or maternal BFR sample. BFR exposure in children was mostly determined via measurements obtained from mothers during lactation or pregnancy, with the exception of one study where samples were obtained from adolescents (12–19 years) (Chen et al., 2011). Study characteristics by five sub group health categories are presented in Tables 1–5. In addition, the general findings from each article were summarised in the ‘Study results’ column of Tables 1–5. Among the 36 included studies, one study (Gascon et al., 2011) examined two health effects, and hence results of this study were presented for two health outcomes (Tables 1 and 5).

3.3. Summary of health effects

The health effects associated with exposure to BFRs were summarised into five sub groups: (1) thyroid disorders (2) diabetes (3) reproductive health (4) cancers and (5) neurobehavioral and developmental disorders. Chemical concentrations of BFRs varied from 0.2 to 85.8 ng per gram of lipid (ng/g lipid). Studies varied in sample size, ranging from a total of 25 participants in the study by Zota et al. (2011) to 1384 participants in the Michigan cohort by Vasiliiu et al. (2006) (Tables 1–5).

3.4. Results of individual studies and risk of bias within studies

3.4.1. Thyroid disorders

In total, nine epidemiological studies for thyroid disorders were extracted (Bloom et al., 2008; Herbstman et al., 2008; Chevrier et al., 2010; Chevrier et al., 2011; Eggesbo et al., 2011; Gascon et al., 2011; Stapleton et al., 2011; Yard et al., 2011; Zota et al., 2011). Eight epidemiological studies for alterations in thyroid hormone levels and PBDEs, and one for thyroid disease and PBB (Yard et al., 2011) were examined (Table 1).

Zota et al. (2011) identified that the sum of PBDEs were associated with increased TSH levels in pregnant women in Northern and Central California during the second trimester (β = 0.40, 95%
<table>
<thead>
<tr>
<th>First author, and publication year</th>
<th>Country</th>
<th>Sample</th>
<th>Total sample size (N)</th>
<th>Age range of study population (years)</th>
<th>BFR/health effects</th>
<th>Method of assessing health outcomes</th>
<th>Study results</th>
<th>Adjustment for confounders</th>
<th>Exposure assessment/method/analysis</th>
<th>Chemical concentration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloom et al. (2008)</td>
<td>USA</td>
<td>Great Lakes anglers in New York (non-Hispanic White)</td>
<td>36</td>
<td>29–45</td>
<td>PBDE/thyroid function</td>
<td>TSH measurement</td>
<td>TSH and PBDE 47, (β: −0.007, 95%CI: −0.219, 0.205)</td>
<td>No association between TSH and PBDE 47</td>
<td>Age, BMI, physician-diagnosed goitre or thyroid condition, use of thyroid-active pharmaceuticals at the time of blood donation having ever worked with or near plastics</td>
<td>Blood serum/GC-HRMS</td>
<td>Sum PBDE: median 15.0 ng/g lipid</td>
</tr>
<tr>
<td>Chevrier et al. (2010)*</td>
<td>USA</td>
<td>Pregnant women received prenatal care at one of six clinics from the center for the health assessment of mothers and children of Salinas, California</td>
<td>270</td>
<td>18–45</td>
<td>PBDE/TSH hormone</td>
<td>Lipids and TSH measurements</td>
<td>TSH and sum PBDEs, Ranged from (β: 10.9, 95%CI: −20.6, 0.0) to (β: 18.7, 95%CI: −29.2, −4.5) Decreased TSH levels with increased levels of PBDEs and BDE 28, 47, 99, 100 and 153</td>
<td>No association between TSH and PBDE 47</td>
<td>Lipids and TSH measurements</td>
<td>Blood serum/GC-IDHRMS</td>
<td>Sum PBDE: mean 26.5 ng/g lipid median 25.2 ng/g lipid LOD range 0.2–2.6 ng/g lipid</td>
</tr>
<tr>
<td>Chevrier et al. (2011)*</td>
<td>USA</td>
<td>Pregnant women received prenatal care at one of six clinics from the center for the health assessment of mothers and children of Salinas, California (279 Latina out of 289)</td>
<td>289</td>
<td>18–45</td>
<td>PBDE/TT3 neonatal TSH</td>
<td>TSH measurement, medical records</td>
<td>TSH and Total serum PBDE, (β: 0.00, 95%CI: −0.06, 0.06)</td>
<td>No association between TSH and Total serum PBDE</td>
<td>Lipids and TSH measurements</td>
<td>Blood serum/GC-HRMS</td>
<td>Sum PBDE: mean 15.3 ng/g lipid median 15.2 ng/g lipid LOD range 0.2–2.6 ng/g lipid</td>
</tr>
<tr>
<td>Eggesbo et al. (2011)*</td>
<td>Norway</td>
<td>Population based</td>
<td>239</td>
<td>–</td>
<td>PBDE/HBCD/TSH in neonates</td>
<td>TSH measurement</td>
<td>BDE 47 If 0.52–0.750 level (β: 0.06, 95%CI: −0.14, 0.26) If 0.751–0.950 level, (β: −0.07, 95%CI: −0.26, 0.13) No association between TSH and BDE 47</td>
<td>No association between TSH and Total serum PBDE</td>
<td>Lipids and TSH measurements</td>
<td>Human milk/GC-ECMS</td>
<td>Sum PBDE: mean 1.7 ng/g lipid median 0.95 ng/g lipid LOD range 0.15–56 ng/g lipid</td>
</tr>
<tr>
<td>Gascon et al. (2011)*</td>
<td>Spain</td>
<td>Invited 4 years 470 mother-child pairs in Menorca birth cohort</td>
<td>470</td>
<td>4 years only for children</td>
<td>PBDE/alteration in thyroid hormone</td>
<td>TSH measurement</td>
<td>PBDE 47 and TT3 hormone levels, (postnatal β: 7.3, 95%CI: −0.4, 14.9) No association between TT3 and PBDE 47</td>
<td>No association between TSH and PBDE 47</td>
<td>Lipids and TSH measurements</td>
<td>Cord blood, Blood serum/GC-ECD, GC-MS</td>
<td>Cord blood serum/GC-MS</td>
</tr>
<tr>
<td>Herbstman et al. (2008)*</td>
<td>USA</td>
<td>Women delivering at Johns Hopkins Hospital</td>
<td>92</td>
<td>14–43 (maternal age)</td>
<td>PBDE/alteration in neonatal thyroid hormone</td>
<td>TSH measurement</td>
<td>BDE 47 TSH (OR: 0.39, 95%CI: 0.19, 0.78), TT4 (OR: 1.46, 95%CI: 0.82, 2.59) FT4 (OR: 1.79, 95%CI: 0.94, 3.40) T4 (OR: 1.64, 95%CI: 0.83, 3.24) Decreased TT3 and FT4 with BDEs Increased TSH with BDEs</td>
<td>No association between TSH and PBDE 47</td>
<td>Lipids and TSH measurements</td>
<td>Cord blood, Blood serum/GC-MS</td>
<td>Cord blood serum/GC-MS</td>
</tr>
<tr>
<td>First author, and publication year</td>
<td>Country</td>
<td>Sample size (N)</td>
<td>Age range of study population (years)</td>
<td>BFR/health effects</td>
<td>Method of assessing health outcomes</td>
<td>Study results</td>
<td>Adjustment for confounders</td>
<td>Exposure assessment-chemical concentration</td>
<td>Study type</td>
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<tr>
<td>Stapleton et al. (2011)*</td>
<td>USA</td>
<td>Pregnant women receiving prenatal care at two clinics in Durham County, North Carolina (80% of the women were non-Hispanic black)</td>
<td>140</td>
<td>18–39</td>
<td>PBDE/alteration in thyroid hormone</td>
<td>TSH and lipids measurement</td>
<td>BDE 47 T4 (β: 0.42, 95%CI: 0.05, 0.78), FT4 (β: 0.05 , [1], [2], [5], [7], [10] 95%CI: 0.01, 0.08) TSH (β: 0.07 , 95%CI: 0.02, 0.16) TT3 (β: 0.04 , 95%CI: 0.01, 0.08) FT3 (β: 0.01, 95%CI: −0.01, 0.01) Increased free and total T4 levels with BDE 47, 99 and 100 Increased TTT, with BDE 47</td>
<td>Blood serum/LC-MS-MS</td>
<td>PBDE 47: mean 16.5 ng/g lipid range 2.0–297.45 ng/g lipid</td>
<td>Prospective cohort</td>
<td></td>
</tr>
<tr>
<td>Yard et al. (2011)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>1,056 female and 1,808 males</td>
<td>1 month–85 years at PBB exposure</td>
<td>PBDE/incidence of thyroid diseases</td>
<td>Medical record confirmation on thyroid diseases</td>
<td>If PBB level: 1.1–2.5, (OR: 0.79, 95%CI: 0.49–1.27) If PBB level: 2.6–6.0, (OR: 1.29, 95%CI: 0.84–1.99) No association between thyroid disease and increased levels of PBB</td>
<td>Blood serum/GC-ECD</td>
<td>Blood range: &lt;1.0 to &gt;6.1 ppb</td>
<td>Nested case control</td>
<td></td>
</tr>
<tr>
<td>Zota et al. (2011)*</td>
<td>USA</td>
<td>Pregnant women in the second trimester in a hospital of California</td>
<td>25</td>
<td>16–45</td>
<td>PBDE/thyroid function</td>
<td>TSH measurements</td>
<td>BDE 207 and TSH: (β: 0.72, 95%CI: −1.10, −0.34)</td>
<td>Blood serum/GC-HRMS</td>
<td>Blood median 85.8 ng/g lipid</td>
<td>Cross-sectional</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: Thyroid hormone (TH), thyroxine (T4): free T4 (fT4), total T4 (TT4), triiodothyronine (T3), limit of detection (LOD), not given (NG), body mass index (BMI).

First author and publication year: ‘*‘; Children-related studies.

Confounders:

Exposure assessment:
Gas chromatograph isotope dilution high-resolution mass spectrometry (GC-IDHRMS), gas chromatograph high resolution mass spectrometer (GC-HRMS), gas chromatograph electron capture detector (GC-ECD), chromatograph electron capture mass spectrometry (GC-ECMS), liquid chromatograph mass spectrometry, mass spectrometry (LC/MS-MS), high resolution gas chromatograph interfaced with a high resolution mass spectrometer (HRGC-HRMS).

Chemical concentration:
Mean concentration of sum PBDE or BDE 47 (if absence of sum PBDE) were reported, or range of the PBDE or PBB concentration were reported if there is no mean.
### Table 2

Study characteristics for diabetes (N = 3).

<table>
<thead>
<tr>
<th>First author, and publication year</th>
<th>Country</th>
<th>Sample</th>
<th>Total sample size (N)</th>
<th>Age range of study population (years)</th>
<th>BFR/health effects</th>
<th>Method of assessing health outcomes</th>
<th>Study results</th>
<th>Adjustment for confounders</th>
<th>Exposure assessment matrix/analysis</th>
<th>Chemical concentration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (2010)</td>
<td>USA</td>
<td>Population based</td>
<td>90 55 case/69 control</td>
<td>20–36</td>
<td>PBB/type 2 diabetes</td>
<td>Clinical measurements for fasting glucose, triglycerides, total cholesterol</td>
<td>Model 1 (OR: 3.0, 95%CI: 1.1, 8.1)</td>
<td>Model 1 [1], [2], [3] and race at 2 years</td>
<td>Blood serum/GC-IDHRMS</td>
<td>PBB 1st quartiles: percentiles values: &lt;9 pg/g CRDIA</td>
<td>Nested case control</td>
</tr>
<tr>
<td>Turyk et al. (2009)</td>
<td>USA</td>
<td>Great Lakes sport fish consumers</td>
<td>503</td>
<td>0-70</td>
<td>PBDE/diabetes in persons with hypothyroid disease</td>
<td>Hemoglobin HbA1c measurement by quest diagnostics</td>
<td>(OR: 0.9, 95%CI: 0.5–0.7)</td>
<td>Model 2 (further adjustment for triglyceride and total cholesterol at year 2)</td>
<td>Blood serum/GC–MS</td>
<td>Blood serum range &lt;LOD–10.1 ng/g lipid</td>
<td>Cross-sectional</td>
</tr>
<tr>
<td>Vasiliu et al. (2006)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>1384</td>
<td>20–60</td>
<td>PBB/adult-onset diabetes</td>
<td>GC-ECD/self reporting</td>
<td>If PBB level: 1.1–3.0, (IDR: 0.71, 95%CI: 0.33–1.56) in men ( IDR: 1.08, 95%CI: 0.61–1.89) in women</td>
<td>Blood serum/GC–ECD</td>
<td>Blood serum range: LOD–7 ppb</td>
<td>Retrospective cohort</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:**
- LOD: Limit of detection
- NG: not given
- BMI: body mass index

**Confounders:**
- [1] Age
- [2] gender
- [3] BMI
- [4] smoking
- [5] alcohol use

**Exposure assessment:**
- GC-IDHRMS: gas chromatograph isotope dilution high-resolution mass spectrometry
- GC–MS: gas chromatograph mass spectrometer
- GC–ECD: gas chromatograph electron capture detector

**Chemical concentration:**
- Mean concentration of sum PBDE or BDE 47 (if absence of sum PBDE) were reported, or range of the PBDE or PBB concentration were reported if there is no mean.
<table>
<thead>
<tr>
<th>First author, and publication year</th>
<th>Country</th>
<th>Sample</th>
<th>Total sample size (N)</th>
<th>Age range of study population (years)</th>
<th>BFR/health effects (N= 17)</th>
<th>Method of assessing health outcomes</th>
<th>Study results</th>
<th>Adjustment for confounders</th>
<th>Exposure assessment matrix/analysis</th>
<th>Chemical concentration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanck et al. (2002)*</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>308</td>
<td>5–24</td>
<td>PBB/height and weight in girls exposed in utero and postnatally</td>
<td>Self-reported height and weight</td>
<td>Height if &gt;1.0–7.0 ppb PBB, (β: −0.33, 95%CI: −1.0, 0.4) if &gt; 7.0 ppb PBB, (β: 0.61, 95%CI: −0.50, 1.7)</td>
<td>Weight if &gt;1.0–7.0 ppb PBB, (β: 8.67, 95%CI: 1.0, 16.0) if &gt;7.0 ppb PBB, (β: 0.50, 95%CI: −11.2, 11.8)</td>
<td>Blood serum/GC-ECD</td>
<td></td>
<td>median: 1.1 ppb</td>
</tr>
<tr>
<td>Blanck et al. (2000)*</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>327</td>
<td>5–24</td>
<td>PBB/earlier pubic hair stage in breastfed girls in perinatal PBB exposure</td>
<td>Self-assessment of pubertal and breast development by use of Tanner stage schematic drawings</td>
<td>An earlier menarche in women with high estimated serum PBB level at the time of pregnancy (&gt;7 ppb) than low PBB level (HR: 3.40, 95%CI: 1.27, 9.04)</td>
<td>Self-assessed tanner breast stage in daughters in low PBB exposure (OR: 0.7, 95%CI: 0.3–1.6)</td>
<td>Blood serum/GC-ECD</td>
<td></td>
<td>mean: 17.3 ppb</td>
</tr>
<tr>
<td>Blank et al. (2004)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>990</td>
<td>24–79</td>
<td>PBB/time to menopause</td>
<td>Self-reported time to menopause via questionnaires</td>
<td>No statistical results showed with time to menopause</td>
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<tr>
<td>Carmichael et al. (2010)*</td>
<td>USA</td>
<td>Population based in California</td>
<td>48 (20 case/28 control)</td>
<td>25–35</td>
<td>PBDE/ Hypospadias a</td>
<td>Medical record confirmation by California birth defect monitoring program</td>
<td>PBDE 47: (OR: 1.01, 95%CI: 0.93, 1.11)</td>
<td></td>
<td></td>
<td>Blood serum/GC-IDHRMS</td>
<td></td>
</tr>
<tr>
<td>Chao et al. (2010)</td>
<td>Taiwan</td>
<td>Population based from four hospitals from southern Taiwan</td>
<td>46</td>
<td>21–41</td>
<td>PBDE/ menstruation characteristics of reproductive age females</td>
<td>Detailed questionnaires</td>
<td>Women with duration of menstrual bleeding cycle &gt;5 days (age-adjusted OR: 0.994, 95%CI: 0.990, 0.999)</td>
<td>Prolonged length of the longest menstrual cycle, Log BDE 99 (β: 0.193, p = 0.028)</td>
<td></td>
<td>Human milk/HRC, HRMS</td>
<td></td>
</tr>
<tr>
<td>Chen et al. (2011)*</td>
<td>USA</td>
<td>Population based</td>
<td>271</td>
<td>12–19</td>
<td>PBDE/earlier ages at menarche f</td>
<td>Questionnaires</td>
<td>Menarche &lt;12 years (RR: 1.60, 95%CI: 1.12, 2.28)</td>
<td>Menarche &lt;11 years (RR: 1.39, 95%CI: 0.59, 3.24)</td>
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<tr>
<td>Davis et al. (2005)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>337</td>
<td>24–56</td>
<td>PBDE/ menstrual function</td>
<td>Self-reported menstrual function</td>
<td>Menstrual cycle length by weight loss (RR: −3.55, 95%CI: −6.45, −0.65)</td>
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</table>

(continued on next page)
### Table 3 (continued)

<table>
<thead>
<tr>
<th>First author, and publication year</th>
<th>Country</th>
<th>Sample size (N)</th>
<th>Total sample size (N)</th>
<th>Age range of study population (years)</th>
<th>BFR/health effects</th>
<th>Method of assessing health outcomes</th>
<th>Study results</th>
<th>Adjustment for confounders</th>
<th>Exposure assessment-matrix/analysis</th>
<th>Chemical concentration</th>
<th>Study type</th>
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</thead>
<tbody>
<tr>
<td>Givens et al. (2007)*</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>899</td>
<td>15–44 (maternal age) – (infants)</td>
<td>PBDE/infant birth weight and gestational age</td>
<td>Birth weight, gestational age measurement through electronic birth certificate information</td>
<td>Birth weight (β: 27.25, 95% CI: –110.05, 164.55); Gestational age (β: 0.224, 95% CI: –0.295, 0.743)</td>
<td>[7], [8], [9], [12], [13], [17], alcohol ingestion, prenatal care, maternal medical risks</td>
<td>Blood serum/GC-ECD</td>
<td>range: 1.0–3.38</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Harley et al. (2011)*</td>
<td>USA</td>
<td>Pregnant women living in low income region of Salinas Valley in California (predominantly Hispanic)</td>
<td>286</td>
<td>&lt;20 to ≥35 (maternal age)</td>
<td>PBDE/infant birth weight</td>
<td>Birth weight measurement, prenatal and delivery medical record</td>
<td>BDE 47 (β = –115 g, 95% CI: –229, –2) BDE 99 (β = –114 g, 95% CI: –225, –4)</td>
<td>[13], [2], [3], [7], [8]</td>
<td>Blood in serum/GC</td>
<td>BDE 47-25th percentile: median 7.78 ng/g lipid</td>
<td>Retrospective cohort</td>
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<tr>
<td>Harley et al. (2010)</td>
<td>USA</td>
<td>Pregnant women living in low income region of Salinas Valley in California (predominantly Mexican-immigrants)</td>
<td>223</td>
<td>21–27.3</td>
<td>PBDE/time to pregnancy</td>
<td>In person interview time to pregnancy</td>
<td>BDE-100 (OR: 0.6, 95% CI: 0.4–0.9) BDE-153 (OR: 0.5, 95% CI: 0.3–0.8); Sum of BDEs 47, 99, 100, 153 (OR: 0.7, 95% CI: 0.5–1.0)</td>
<td>[4], [9], [12], country of birth, years of residence in the US, alcohol, drug use during pregnancy, marital status</td>
<td>Blood serum/GC-IDHRMS</td>
<td>PBDE 47: mean 14.9 ng/g lipid</td>
<td>Retrospective cohort</td>
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<td>Hoffman et al. (2007)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>943</td>
<td>–</td>
<td>PBB/endometriosis g</td>
<td>Self-reported and medical records of endometriosis</td>
<td>Moderate PBB exposure (1–4 ppb) (HR: 0.72, 95% CI: 0.39, 1.31) High PBB exposure (&gt;4 ppb) (HR: 0.90, 95% CI: 0.51, 1.59) (HR: 1.61, 95% CI: 1.19, 2.17)</td>
<td>[1], [3]</td>
<td>Blood serum/GC-ECD</td>
<td>median: 1–4 ppb range: 0.5–1745</td>
<td>Retrospective cohort</td>
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<tr>
<td>Jamieson et al. (2011)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>956</td>
<td>24 to ≥50</td>
<td>PBBD/risk of reporting an abnormal pap test</td>
<td>Self-reported and medical records of an abnormal pap test</td>
<td>[1], [2], [3], [4], [7], [16], history of [1] regularly, duration health insurance status, history of diethylstilbestol exposure, lifetime duration of oral contraceptive use, history of cervical cancer [1], [17], [11], [3], [4], [2], [16], menopause status, oral contraceptive medicine</td>
<td>Blood serum/GC-ECD</td>
<td>Blood serum/GC-ECD</td>
<td>range: 1–12 ppb</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Kaiser et al. (2003)</td>
<td>USA</td>
<td>Michigan Cohort</td>
<td>951</td>
<td>&lt;1–62</td>
<td>PBB/self-reported physician-diagnosed benign breast disease</td>
<td>Structured questionnaires, self-physician report benign breast disease</td>
<td>Moderate PBB exposure (1–12 ppb) (OR: 1.08, 95% CI: 0.80–1.45); High PBB exposure (&gt;12 ppb) (OR: 0.79, 95% CI: 0.46–1.38)</td>
<td>Blood serum/GC-ECD</td>
<td>range: 1–12 ppb</td>
<td>Retrospective cohort</td>
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<tr>
<td>Small et al. (2007)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>529</td>
<td>20–35</td>
<td>PBBD/risk of spontaneous abortion</td>
<td>Self-reporting, medical records, telephone interview</td>
<td>If 1–2.9 ppb PBB, (OR: 1.05, 95% CI: 0.67, 1.63) If ≥2.9 ppb PBB, (OR: 0.73, 95% CI: 0.47, 1.13)</td>
<td>[2], [6], [7], [3], [4], [2], [16], history of spontaneous abortion prior to accident, infertility, self-reported physician diagnosis of pelvic inflammatory disease, age at menarche</td>
<td>Blood serum/GC-ECD</td>
<td>range: LOD-2.9 ppb</td>
<td>Retrospective cohort</td>
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<tr>
<td>Small et al. (2009)*</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>464</td>
<td>5–30</td>
<td>PBBD/genitourinary (GU)conditions-hernia b or hydrocele c, hypospadiasa, cryptorchidism d</td>
<td>Self-reporting genitourinary conditions</td>
<td>Any GU in maternal PBB level with &gt;5.0 ppb (OR: 2.0, 95% CI: 0.78–5.1)</td>
<td>[5], [6], birth weight</td>
<td>Blood serum/GC-ECD</td>
<td>range: LOD-2.9 ppb</td>
<td>Retrospective cohort for younger sons: mean 10.9 ppb range LOD-361 ppb</td>
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<td></td>
<td>Hernia or hydrocele in maternal PBB level with &gt;5.0 ppb (OR: 6.16, 95% CI: 0.5, 42.5)</td>
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<tr>
<td>First author, and publication year</td>
<td>Country</td>
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<td>Study results</td>
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<td>Exposure assessment/method/analysis</td>
<td>Chemical concentration</td>
<td>Study type</td>
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<tr>
<td>Sweeney and Symaski (2007)*</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>560 mothers and 1, 111 offsprings</td>
<td>&lt;10–42 (maternal age at PBB exposure)</td>
<td>PBB/birth outcomes</td>
<td>Detailed questionnaires, birth outcome measurements</td>
<td>Infant birth weight: (estimated regression coefficient: 225 g, p = 0.012)</td>
<td>[3], [5], [7], [8], [12], [15] at delivery, internal between the initial serum test and date of delivery</td>
<td>Blood serum/GC</td>
<td>&lt;10 years: mean 31.4 ppb range 1–1490 ppb 11–16 years: mean 20.0 ppb range 0–423 ppb 17–42 years: mean 10.3 ppb range 0–1150 ppb median: 2 µg/L for mothers, 6 µg/L for fathers</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Terrell et al. (2009)*</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>865</td>
<td>–</td>
<td>PBB/ratio of male birth</td>
<td>Sex ratio measurement by birth certificates</td>
<td>Paternal PBB model for a 10 µg/L increase in the natural log of paternal PBB concentration (AOR: 1.15, 95%CI: 0.08, 1.65) Maternal and paternal PBB model a 10 µg/L increase in the natural log of maternal PBB concentration (AOR: 1.06, 95%CI: 0.97, 1.17)</td>
<td>Parental [3] at cohort enrolment, birth order [5], [9], [15] at offspring's birth year of offspring's birth Blood serum/GC-ECD</td>
<td>Retrospective cohort</td>
<td></td>
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**Abbreviation:**
- LOD: Limit of detection
- LOD: Limit of quantification
- BMI: Body mass index
- PBB: Polybrominated biphenyls
- PBDE: Polybrominated diphenyl ether
- LOD: Limit of detection (LOD), not given (NG), body mass index (BMI).
- First author and publication year: ‘*’; children-related studies.
- Confounders:
- Exposure assessment:
  - Gas chromatograph isotope dilution high-resolution mass spectrometry (GC-IDHRMS), gas chromatograph (GC), gas chromatograph electron capture detector (GC-EDC), high resolution gas chromatograph interfaced with a high resolution mass spectrometer (HRGC-HRMS).
- Chemical concentration:
- Mean concentration of sum PBDE or BDE 47 (if absence of sum PBDE) were reported, or range of the PBDE or PBB concentration were reported if there is no mean. Sample: ‘*’; Children-related studies.
- BFR/health effects:
  - Hypospadias: birth defect of male urethra that abnormally placed urinary meatus b. Hernia: the protrusion of an organ or the fascia of an organ through the wall of the cavity c. Hydrocele: accumulation of fluids around a testicle. d. Cryptorchidism: absence of one or both testes e. Menarche: the first menstrual bleeding or cycle f. Endometriosis: the presence of functioning endometrial glands and stroma outside of the uterus.
<table>
<thead>
<tr>
<th>First author, and publication year</th>
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<th>Total Sample size (N)</th>
<th>Age range of study population (years)</th>
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<th>Study results</th>
<th>Adjustment for confounders</th>
<th>Exposure assessment/method/analysis</th>
<th>Chemical concentration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardell et al. (2009)</td>
<td>Sweden</td>
<td>Population based</td>
<td>99 cases/99 control</td>
<td>19–75 (case) 21–73 (control)</td>
<td>PBDE/Diagnosis of non-Hodgkin lymphoma</td>
<td>IgG antibody measurement</td>
<td>(OR: 0.7, 95%CI: 0.4–1.2)</td>
<td>[1], [2], sex</td>
<td>Blood plasma/HRGC, HRMS</td>
<td>BDE 47: mean 2.8/2.7 ng/g lipid (case/control) median 1.5/1.8 ng/g lipid (case/control)</td>
<td>Case-control</td>
</tr>
<tr>
<td>Hardell et al. (2006)</td>
<td>Sweden</td>
<td>Population based</td>
<td>58 cases/61 controls</td>
<td>Not given, but mentioned less than 55 years old 19–70</td>
<td>PBDE/testicular cancer</td>
<td>NG</td>
<td>(OR: 2.5, 95%CI: 1.02, 6.0)</td>
<td>[1], [2]</td>
<td>Blood (not specified)/NG</td>
<td>BG Case-control</td>
<td></td>
</tr>
<tr>
<td>Hoque et al. (1998)</td>
<td>USA</td>
<td>Michigan cohort</td>
<td>Cases ranged from 6 to 27 (depending on 13 cancer sites)/696 controls</td>
<td>19–70</td>
<td>PBB/cancer risks</td>
<td>Health survey, cancer registry with diagnosis of cancer</td>
<td>Digestive system cancer risk, If PBB level 4–20 ppb (OR: 8.23, 95%CI: 1.27, 53.3), If PBB level 21–50 ppb (OR: 12.3, 95%CI: 0.80, 191), If PBB level &gt;50 ppb (OR: 22.0, 95%CI: 1.34–392)</td>
<td>Cigarette smoking, alcohol consumption, family history of cancer, and baseline serum PCB level</td>
<td>Blood serum/GC-ECD</td>
<td>Range: not detectable–50 ng/g lipid</td>
<td>Nested case-control</td>
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<tr>
<td>Hurley et al. (2011)</td>
<td>USA</td>
<td>Women with surgical breast biopsy history in the San Francisco Bay area of California</td>
<td>134 (78 cases and 56 controls)</td>
<td>40–60</td>
<td>PBDE/breast cancer</td>
<td>Questionnaires, interview, pathological analyses with biopsy</td>
<td>BDE-47 (OR: 0.56, 95%CI: 0.19–1.68)</td>
<td>[1], race/ethnicity, birthplace, BMI, marital status, family income, education, age at menarche, parity, age at first live birth, lifetime duration of lactation</td>
<td>Breast adipose tissue/GC-MS</td>
<td>BDE 47: median 18.83/26.85 ng/g lipid (case/control)</td>
<td>Case-control</td>
</tr>
</tbody>
</table>

**Abbreviation:**
Limit of detection (LOD), not given (NG), body mass index (BMI).

**Confounders:**

**Exposure assessment:**
High resolution gas chromatograph interfaced with a high resolution mass spectrometer (HRGC-HRMS).
Gas chromatograph high resolution mass spectrometer (GC-MS); gas chromatograph electron capture detector (GC-EDC).

**Chemical concentration:**
Mean concentration of sum PBDE or BDE 47 (if absence of sum PBDE) were reported, or range of the PBDE or PBB concentration were reported if there is no mean.

**BFR/health effects:**
- Hodgkin lymphoma: a type of lymphoma originating from lymphocytes.
<table>
<thead>
<tr>
<th>First author, and publication year</th>
<th>Country</th>
<th>Sample</th>
<th>Total sample size (N)</th>
<th>Age range of study population (years)</th>
<th>BFR/health outcomes</th>
<th>Method of assessing health outcomes</th>
<th>Study results</th>
<th>Adjustment for confounders</th>
<th>Exposure assessment matrix/analysis</th>
<th>Chemical concentration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzgerald et al. (2011)</td>
<td>USA</td>
<td>Men and women between 55 and 74 years of age who lived in Hudson Falls, Fort Edward, or Glens Falls, New York for at least 25 years</td>
<td>144</td>
<td>55–74</td>
<td>PBDE/neuropsychological status</td>
<td>Neuropsychology assessment (NART-R, TOMM, CVLT, WMS, SCWT, WCST, WMSS, GPT, FTT, BDI, STA)</td>
<td>Worse scores on the long-delay free recall (β: -0.096 per unit change in log-transformed lipid basis total PBDE, p = 0.014)</td>
<td>Age, gender, education, income, NART-R score, BMI, smoking, alcohol consumption, health conditions, occupational or hobby exposure to lead, mercury</td>
<td></td>
<td>Sum PBDE: mean 86.1 ng/g lipid</td>
<td>Cross-sectional</td>
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<tr>
<td>Gascon et al. (2011)*</td>
<td>Spain</td>
<td>Invited 4 years 470 mother-child pairs in Menorca birth cohort</td>
<td>470</td>
<td>4 years only</td>
<td>PBDE/alteration in neurodevelopment and thyroid hormone</td>
<td>GC-ECD, GC-MS/ neurodevelopment assessment (MSCA, ADHD-DSM-IV, CP-SCS)</td>
<td>Discriminability: (β: -0.019, p = 0.010) CVLT t-score (β: -2.009, p = 0.059)</td>
<td>[1], [2], [3], [4], alcohol, evaluating psychologist</td>
<td>Cord blood serum/GC-ECD, GC-MS</td>
<td></td>
<td>Cord blood PBDE 47: median 0.12 ng/g lipid</td>
</tr>
<tr>
<td>Herbstman et al. (2010)*</td>
<td>USA</td>
<td>Pregnant women delivered at one of three hospitals in world trad center area</td>
<td>96</td>
<td>12–48 months, 72 months</td>
<td>PBDE/neurodevelopment</td>
<td>Developmental assessment: BSID-II, MDI, PDI, WPPSI-R</td>
<td>PBDE 47 and Cognitive and motor functions, (β: -2.7, 95%CI: -7.0, 1.6) for postnatal exposure (β: -1.4, 95%CI: -9.2, 6.5)</td>
<td>PBDE 47 and poor social competence symptoms (RR: 2.6, 95%CI: 1.2, 5.9)</td>
<td>Cord blood PBDE 47: median 11.2 ng/g lipid</td>
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<td>Prospective cohort</td>
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<tr>
<td>Hertz-Picciotto et al. (2011)*</td>
<td>USA</td>
<td>Population based in California</td>
<td>94</td>
<td>2–5</td>
<td>PBDE/diagnosis of autism</td>
<td>ADOS, ADI-R, MSEL, VABS, SQC, EDQ</td>
<td>BDE 47 (OR: 0.75, 90%CI: 0.40, 1.42) &amp; 48-month Full IQ (BDE 47 100, 95%CI: 1.0, 3.2) &amp; 72-month Full and Performance IQ (BDE 100 and 153)</td>
<td>[1], [2], [3], [5], father’s age, number of computers in the household, child, BMI, calendar time, and consumption of ocean fish</td>
<td>Whole Blood/GC-HRMS</td>
<td></td>
<td>PBE 47 25th Case-control percentile: 3.56 ng/g lipid</td>
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</table>

**Abbreviation:**
- Body mass index (BMI)
- First author and publication year: "*"; children-related studies.
- **Exposure assessment:**
  - Gas chromatograph high resolution mass spectrometer (GC-HRMS), gas chromatograph electron capture detector (GC-ECD), gas chromatograph mass spectrometry (GC-MS), high resolution gas chromatograph interfaced with a high resolution mass spectrometer (HRGC-HRMS).
- **Chemical concentration:**
  - Mean concentration of sum PBDE or BDE 47 (if absence of sum PBDE) were reported, or range of the PBDE or PBB concentration were reported if there is no mean. Sample: "*"; Children-related studies with a term of that referred to babies, neonates, children; studies with under 18 years old population, prenatal exposure or pregnant women that may influence children's health were also included.
- **Method of health outcome assessment:**
  - The McCarthy Scales of Children's Abilities (MSCA), the attention-deficit hyperactivity disorder criteria of the diagnostic and statistical manual of mental disorders 4th edition (ADHD-DSM-IV), the California preschool social competence scale (CP-SCS), the new adult reading test-revised (NART-R), the test of memory malingering (TOMM), the stroop color-word test (SCWT), Wisconsin card sorting test (WCST), the California verbal learning test (CVLT), the Wechsler memory scale (WMS), the static motor steadiness test (SMST), the grooved pegboard test (GPT), the finger tapping test (FFT), the beck depression inventory (BDI), the state-trait anxiety inventory (STAI), the Bayley scales of infant development, second edition (BSID-II), mental development index (MDI), psychomotor development index (PDI), the Wechsler preschool and primary scale of intelligence, revised edition (WPPSI-R), autism diagnostic observation schedules (ADOSs), the autism diagnostic interview-revised (ADI-R), mullen scales of early learning (MSLE), vineland adaptive behavior scales (VABS), the social communication questionnaire (SCQ), the early development questionnaire (EDQ), immunoglobulin G (Ig G), the attention-deficit hyperactivity disorder (ADHD).
This study also found that decreased TSH was related to PBDE-207 ($\beta = -0.72$, 95% CIs = $-1.10$ to $-0.34$) whereas there was a weak and inconsistent association between PBDEs and free T$_4$ ($\beta = -0.02$, 95% CIs = $-0.15$ to $0.12$) and total T$_4$ ($\beta = 0.50$, 95% CIs = $-1.04$ to $2.04$) (Zota et al., 2011). As this was a pilot study with a sample size of 25, the results may be difficult to generalise. Stapleton et al. (2011) also reported a finding of an association between PBDE exposure and TSH during pregnancy. It was observed that PBDE 47, 99 and 100 were correlated with elevated levels of free and total T$_4$. Furthermore, positive associations were seen between increased levels of total triiodothyronine (TT$_3$: 178 ng per deciliter (ng/dL)) and PBDE-47 (OR = 1.30, 95% CIs = 1.00–1.69), and a negative relationship between TT$_3$ and 4-hydroxylated PBDE-49 (4-OH-BDE-49) (OR = 0.51, 95%CIs = 0.30–0.86) (Stapleton et al., 2011). Interestingly, there were higher PBDE levels in non-Hispanic blacks compared to non-Hispanic whites and PBDE levels decreased with age (Stapleton et al., 2011). Evidence also emerged for an association between PBDEs and neonatal thyroid hormone levels. Herbstman et al. (2008) found no statistically significant relationship between total thyroxine measured in blood spots collected after birth and cord serum concentrations of PBDE 47, 100 or 153. In children born by unassisted vaginal delivery, increased odds of low total thyroxine at 18 days of age but not at 2 days of age were associated with cord PBDE-153 (Herbstman et al., 2008). In addition, TSH levels decreased with increased levels of PBDEs and PBDE 28, 47, 99, 100 and 153 concentrations in the sera of pregnant women around 27 weeks of gestation (Chevrier et al., 2010). Odds of subclinical hyperthyroidism were also elevated with increased exposure to BDE 100 and BDE 153 (Chevrier et al., 2010).

Increased levels of PBB after BMI adjustment were not statistically related to the incidence of thyroid diseases but women with thyroid disease were at an increased risk of developing diabetes (OR = 1.61, 95% CIs = 1.04–2.51) (Yard et al., 2011). Gascon et al. (2011) also indicated that the concentration of pre- and post-natal PBDEs was not related to alteration in thyroid hormone levels in children at 4 years of age from the USA. Three studies that examined PBDE exposure and alterations in thyroid hormone in neonates (Chevrier et al., 2011; Eggesbo et al., 2011), and in recreational fishermen (Bloom et al., 2008) found no statistically significant association although further investigation was recommended (Bloom et al., 2008).

### 3.4.2. Diabetes

Three epidemiological studies examined PBDE and PBB exposure and diabetes (Vasiliu et al., 2006; Turyk et al., 2009; Lee et al., 2010) (Table 2). Turyk et al. (2009) reported that there were no obvious associations between PBDEs and diabetes. However, the authors suggested that body burden of sum PBDEs can influence the impact of diabetes in persons with hypothyroid disease (Turyk et al., 2009). Lee et al. (2010) also found that PBB 153, the only PBB analysed, was linked to an increased risk of type 2 diabetes in the second (OR = 3.0, 95% CIs = 1.1–8.1, 10–16 pg/g PBB exposure) or third quartile (OR = 3.1, 95% CIs = 1.1–9.2, 17–23 pg/g PBB exposure) compared to the lower quartiles of less than 9 pg/g PBB exposure in an adjusted model for age, sex, race and BMI at year 2. The quartiles referred to different serum concentrations of PBB 153 and ranged from <9 picograms per gram (pg/g) in the 1st quartiles to >23 in the 4th quartile (Lee et al., 2010). The Michigan cohort is a cohort group potentially exposed to PBB via a food chain accident (ingestion of contaminated food in the early 1970s). Vasiliu et al. (2006) found no increased risk of developing diabetes among the Michigan cohort after 25 years of follow up. The authors acknowledge that they may have underestimated diabetes incidence in this population as those lost to follow up were older and had a higher BMI which are important risk factors for
3.4.3. Reproductive health effects

This review identified 17 epidemiological studies investigating associations between exposure to BFRs and reproductive health outcomes including: decreased birth weight (Blanck et al., 2002; Givens et al., 2007; Harley et al., 2011; Sweeney and Symanski, 2007); fecundability (the ability to achieve and maintain pregnancy), (Harley et al., 2010); alteration in secondary sex ratio, defined as the proportion of male births (Terrell et al., 2007); spontaneous abortion (Small et al., 2007); alteration in age at menarche and Tanner stage (Blanck et al., 2000); hypospadias (Carmichael et al., 2010); genitourinary conditions (Small et al., 2009); abnormal Pap Smear test (Jameson et al., 2011); changes in menstruation characteristics (Davis et al., 2005; Chao et al., 2010); benign breast disease (Kaiser et al., 2003); time to menarche (Chen et al., 2011), time to menopause (Blanck et al., 2004); and risk of endometriosis (Hoffman et al., 2007) (Table 3).

Direct and indirect effects of BFR exposure and reproductive health on paediatric health outcomes have been reported (Blanck et al., 2000; Chao et al., 2010; Chen et al., 2011; Small et al., 2009; Harley et al., 2010; Harley et al., 2011). Blanck et al. (2000) divided the female participants into 6 groups (breast-fed and non-breast-fed and low, medium and high prenatal BFR exposure).

In the study, breastfed girls who were prenatally exposed to high levels of PBB had earlier development of pubic hair and onset of menarche than breastfed girls who were prenatally exposed to lower levels of PBB (Blanck et al., 2000). This relationship persisted after adjustment for potential confounders (Hazard ratio (HR) = 3.4, 95% CI = 1.27–9.04) (where HR is the ratio of the hazard rates corresponding to the conditions described by the two levels of explanatory variables), (Blanck et al., 2000). Irregular menstrual periods have been correlated with higher concentrations of the sum of PBDE congeners and certain BDE congeners (from 183 to 209) (Chao et al., 2010). There is also evidence that higher concentrations of serum PBDEs (median of sum PBDE; 44.7 ng/g lipid) could be related to earlier ages at menarche (Relative Risk (RR) = 1.60, 95% CI = 1.12–2.28) (Chen et al., 2011). Small et al. (2009) showed that sons of women exposed to high levels of PBB (>5 ppb) were twice as likely to report any male genitourinary condition (hernias, hydroceles, cryptorchidism, hypospadias, varicocele) compared with sons of the least exposed women (<1 ppb; OR = 2.0; 95% CI = 0.8–5.1) after adjustment for gestational age at birth. This risk increased when sons born after the exposure but before the mother’s serum PBB measurement was taken were excluded (OR = 3.1, 95% CI = 1.0–9.1). Harley’s study (2011) concluded that infant birth weights decreased when maternal concentrations of PBDE 47, 99 and 100 were increased. In this study, every 10-fold increase in maternal PBDE-47 concentration was associated with a 115 g decrease in birth weight in a continuous measurement (β = −115.4, 95% CI = −229 to −2). In addition, PBDEs were also found in the serum of 95% of pregnant participants, and could be related to reduced fecundability (Harley et al., 2010). In particular, there was a significantly decreased odds of fecundability for PBDE-100 (OR = 0.6, 95% CI = 0.4–0.9), PBDE-153 (OR = 0.5, 95% CI = 0.3–0.8), and sum of the PBDE congeners in this study (OR = 0.7, 95% CI = 0.5–1.0). In a study of adult women (25–44 years), Davis et al. (2005) reported that there was an association between higher PBB of women with weight loss in the past year and 3.55 days shorter cycle length (95% CI = −6.45 to −0.65) but this data was obtained from a very small sample (N = 4). There was no identified evidence between PBB exposure and menstrual cycle characteristics.

A number of studies found either non-significant or no relationship between BFR concentrations and reproductive health. This included no association between maternal serum PBB and gestational age (Givens et al., 2007; Sweeney and Symanski, 2007) although high levels of maternal serum PBB were related to lower birth weight. Terrell et al. (2009) identified 922 offspring born to 496 Michigan cohort mothers from linkage with electronic birth records and, for 366 of these offspring, they identified 208 fathers who were also participants in the PBB cohort. The authors reported a 6% increase in the odds of a male birth for a 10 µg/L increase in the natural log of combined parental exposure to PBBS which was not statistically significant after adjustment for year of offspring’s birth, parental BMI and offspring born to the same mother or father (OR = 1.06, 95% CI = 0.97–1.17). Small et al. (2007) concluded that there was no risk of spontaneous abortion in 529 women exposed to PBDEs after adjustment for maternal age at conception, age at menarche, and prior infertility described as the inability to achieve pregnancy. There was also no evidence for a relationship between prenatal PBB exposure and height or weight in girls (Blanck et al., 2002). Hypospadias, a congenital malformation in the urethral opening in males, was not statistically correlated with maternal PBDE exposure, but the authors suggested that a larger study might be warranted in order to identify the relationship (Carmichael et al., 2010). Jameson et al. (2011) reported an increased risk for self-reporting an abnormal Pap Smear among highly exposed women (13 µg/L PBB exposure) compared to women with non-detectable PBB exposure after adjustment for polychlorinated biphenyl (PCB) concentrations, age at the interview and smoking history, although it did not reach statistical significance (HR = 1.23, 95% CI = 0.74–2.06). In studies by Hoffman et al. (2007), Blanck et al. (2004), and Kaiser et al. (2003) no evidence was found for an association between PBDE exposure and endometriosis, time to menopause, abnormal Pap test results, or benign breast disease.

3.4.4. Cancers

Exposure effects and cancers were investigated in three case-control studies (Hardell et al., 2006; Hardell et al., 2009; Hurley et al., 2011) and one nested case-control study from the Michigan cohort accidentally exposed to PBB (Hoque et al., 1998). Each study examined different cancers, i.e. Non-Hodgkin lymphoma, testicular cancer, benign breast cancer, digestive system and other cancers. Of these studies, one examined PBB (Hoque et al., 1998) and three examined PBDEs (Hardell et al., 2006; Hardell et al., 2009; Hurley et al., 2011). No study examined paediatric cancer (Table 4).

Non-Hodgkin Lymphoma (NHL), a lymphoid malignancy, was not associated with PBDE exposure (OR = 0.7, 95% CI = 0.4–1.2) after controlling for age, sex and BMI (Hardell et al., 2009). There was no selection bias as the Swedish population registry was used to select participants with no time gap for recruiting the cases and controls (Hardell et al., 2009). In an earlier study, Hardell et al. (2006) investigated in utero exposure to persistent organic pollutants (POPs) and testicular cancer risk, and reported an increased concentration of PBDEs in mothers whose sons were diagnosed with testicular cancer (OR = 2.5, 95% CI = 1.02–6.0). However, a relationship between in utero exposure to PBDEs and testicular cancer was difficult to establish because increased concentrations of PBDEs have been found in the human food chain (Hardell et al., 2006). Thus, the authors further suggested that adjustment for food habits would be required because food consumption (fish, dairy products, meat, poultry and eggs), the main exposure pathway of POPs (approximately 95% of POP exposure comes by food), may have caused an increase in PBDE concentration in mothers (Hardell et al., 2006). A small case-control study by Hurley et al. (2011) found no evidence of a relationship between PBDE concentrations in adipose tissue and the risk of breast cancer. Although Hoque
et al. (1998) reported a 2.4-fold increased breast cancer risk with exposure to PBB levels of 4–20 pbp this was not statistically significant (OR = 2.41, 95% CIs = 0.92–6.30) after adjusting for age, family cancer history, cigarette smoking, alcohol drinking, and baseline serum PCB levels in the multivariate analysis. There was no association between PBB exposure and prostate, lung, larynx, colon, female reproductive system, urinary system, leukaemia, melanoma, and ovarian cancers. However, this study showed an increased dose–response relationship between risk of digestive system cancers and higher serum PBDE in the multivariate analysis. A dose response relationship between PBB concentration and lymphoma was also apparent after univariate analysis (Hoque et al., 1998).

3.4.5. Neurobehavioral and developmental disorders

Four studies explored neurobehavioral and developmental disorders, such as alteration in neurodevelopment, autism, and alteration in neuropsychological status with inconsistent outcomes reported (Herbstman et al., 2010; Fitzgerald et al., 2011; Gascon et al., 2011; Hertz-Picciotto et al., 2011). The number of sample participants varied between 96 and 470 individuals (Table 5).

Key neurobehavioral effects of exposure to different types of PBDEs were examined in three studies (Gascon et al., 2011; Herbstman et al., 2010; Fitzgerald et al., 2011). Gascon et al. (2011) found that postnatal exposure to PBDE-47 was statistically associated with an increased risk of symptoms of the attention deficit sub-scale of Attention Deficit Hyperactivity Disorder (ADHD) symptoms at four years of age (RR = 1.8, 95% CIs = 1.0–3.2), but did not affect hyperactivity symptoms. In a prospective cohort study, Herbstman et al. (2010) recruited women who were pregnant on 11 September 2001 and subsequently delivered around the World Trade Center (WTC), and examined environmental samples from pre-and post-9/11 near the WTC site. A statistically significant association between children exposed to higher levels of PBDE 47, 99 and 100 in their cord blood and a lower score on mental and physical-developmental tests was observed between the ages of 12–48 months, and at age 72 months after adjusting for exact age of the child at testing, ethnicity, IQ of mother, sex of child, gestational age at birth, maternal age, exposure to environmental tobacco smoke, maternal education, material hardship, and breast-feeding (Herbstman et al., 2010). Specifically, for every unit increase in PBDE-47 there was a 2.1–3.1 decrease in points on developmental indices and the increase was statistically significant. Significant associations were reported for 12-month Psychomotor Development Index (PBDE-47, 24-month Mental Development Index (MDI) (PBDE-47, 99, and 100), 36-month MDI (PBDE-100), 48-month full-scale and verbal IQ (PBDE-47, 99, and 100) and performance IQ (PBDE-100), and 72-month performance IQ (PBDE-100) (Herbstman et al., 2010). In a study of older adults in New York, no overall evidence was found between sum PBDEs and neuropsychological status (Fitzgerald et al., 2011). Similarly, there were no significant associations between PBDE exposure and autism and developmental delay although children diagnosed with autism and developmental delay in all control groups had higher levels of PBDEs (Hertz-Picciotto et al., 2011).

4. Discussion

To our knowledge, this is the first systematic review of the scientific literature exploring the human health consequences of BFR exposure. Of the 36 studies examined, 17 paediatric studies were included. Evidence for causality between exposure to BFRs and health outcomes was evaluated within the Bradford-Hill framework, on the grounds of the following important criteria: biological plausibility, the temporal relationship of the association, strength and consistency of the association, evidence of a biological gradient or dose–response relationship, and consideration of alternate explanations (Hill, 1965).

4.1. Plausibility

Animal experiments allow us to assess the biologic plausibility of the associations observed in epidemiologic studies. Overall, there is strong plausibility for a relationship between exposure to BFRs and various outcomes in humans and mechanisms of action have been inferred from animal and in vitro models.

Thyroid hormones, including triiodothyronine (T3) and thyroxine (T4), regulate protein synthesis, metabolism, body growth and development. When released into the bloodstream thyroid hormones can occur bound to transport proteins, or as free T3 (FT3) and free T4 (FT4). Thyroid-stimulating hormone (TSH) regulates the synthesis and secretion of thyroid hormone by the thyroid gland and in turn thyroid hormone negatively influences TSH secretion through a negative feedback loop (Gilbert et al., 2012; Henrichs et al., 2013). TSH levels can also be moderated by the hypothalamus through release of the thyrotropin releasing hormone (TRH). Interactions between the hypothalamo–pituitary–thyroid axis can be inhibited or stimulated by natural physiological responses or by exposure to chemical pollutants, including PBDEs. PBDEs are structurally similar to T4 (Gill et al., 2004) and can cross the placenta and may interfere with thyroid production and receptor binding leading to altered hormone levels. Animal studies have shown that these exposures generally result in decreased T4 levels and or increased TSH levels. For instance, Blake et al. (2011) found increased T3 and T4 concentrations among F1 female offspring of mothers treated by commercial product DE-71.

Thyroid hormones play a critical role in neurodevelopmental processes, such as neurogenesis, cell migration, synaptic development, neuronal growth, and myelination. The foetus cannot produce TSH before the second trimester of pregnancy and is entirely dependent on maternal thyroid hormone. The fetal thyroid begins to function during week 12 of pregnancy, but the maternal thyroid gland contributes thyroid hormone throughout gestation (Gilbert et al., 2012; Henrichs et al., 2013). The developing central nervous system is sensitive to disruption of thyroid homeostasis throughout the embryonic and fetal periods, continuing through early post-natal life. Small fluctuations in thyroid hormone levels at critical windows of susceptibility may have long lasting health consequences and maternal thyroid dysfunction during early pregnancy may affect a child’s cognitive development (Gilbert et al., 2012; Henrichs et al., 2013).

An in vitro study of human neural progenitor cells (hNPCs) (Schreiber et al., 2010), provided evidence that exposure to PBDEs can cause disruption of hNPCs development through endocrine disruption of cellular thyroid signalling. In rats, a relationship between PBDE-47 exposure and learning and memory alteration has been observed (He et al., 2011b). He et al. (2011a) also found that chronic exposure of parent zebrafish to low doses of PBDE-209 led to neurobehavioral changes in their offspring.

Evidence from human cell lines and animal laboratory studies seems to support a possible increased cancer risk in humans. For example, Li et al. (2012) found that PBDE-209 can lead to cancer cell proliferation in breast, cervical and the normal Chinese Hamster Ovary cell lines. National Toxicology Program (NTP, 1986) reported that there was an increased dose–response relationship between deca-BDE and liver neoplastic nodules in rat experiments, and increased acinar cell adenoma of the pancreas was also detected in male rats exposed to high-dose of deca-BDE. Further evidence is that B6CF1 mice fed PBDE-209 had increased incidence of follicular cell hyperplasia of the thyroid gland, which can raise thyroid cancer risk (Capen, 1992; NTP, 1986). The extrapolation of effects from high-dose rodent tests to predict possible risk in
humans following low-dose exposures remains contentious. Barber et al. (2006) investigated the effects of PBDEs (congeners 47, 99, 153, 183 and 209) in the oestrogen-receptor-positive breast carcinoma MCF-7 cell line and found that low-dose PBDE concentrations appeared capable of damaging cell genomes. Although data is limited, PBDEs, through their endocrine-disrupting effects, may exert an effect through a hormonal pathway for hormonally mediated cancers such as that of the breast (Hurley et al., 2011). The International Agency for Research on Cancer (IARC) has classified PBBs as probably carcinogenic to humans with supporting evidence from other relevant data, namely mechanistic similarity with polychlorinated biphenyls classified as carcinogenic to humans (IARC, 2013).

Reproductive health effects and endocrine disruption were increased in rats and fish exposed to PBDEs (Blake et al., 2011; He et al., 2011a). Blake et al. (2011) investigated the low dose effects of the penta-BDE mixture DE-71 on reproductive health and thyroid hormone among pregnant and lactating rats. In addition, chronic low dose PBDE-207 exposure affected parental gonad development and locomotion in F1 offspring (He et al., 2011a). Animal data suggests perinatal PBB exposure may have antiandrogenic effects through increased metabolism and decreased responsiveness to testosterone (Newton et al., 1982). There is also evidence that BFRs may act as environmental diabetogenic pollutants in rat adipocytes (Hoppe and Carey, 2007).

4.2. Temporality

The availability of prospective studies provides evidence of a temporal relationship between exposure to BFRs and later neurodevelopmental effects in children. In a prospective study, associations between prenatal exposure to PBDEs and subsequent lower scores on mental and physical developmental tests in children were statistically significant (Herbstman et al., 2010). Using a prospective design and data from the Michigan cohort, Small et al. (2009) also showed that women who were accidentally exposed to PBBS from 1973 to 1974 subsequently exposed sons in utero and then linked these exposures to self-reported genitourinary conditions in the sons. The association between PBB and genitourinary conditions was stronger among sons with whom PBB exposure was estimated forward to the time of conception using a decay model. Unfortunately, this study may have been subject to reporting bias in those mothers and sons may be more likely to report a genitourinary condition if they had higher PBB exposure as all participants were informed of their serum PBB level at enrollment. For diabetes, however, two prospective studies report conflicting results. In a 25 year follow up analysis of the Michigan cohort, Vasiliiu et al. (2006) did not find an association between PBB serum levels at enrollment and self-reported diabetes incidence. In a nested case control study, however, Lee et al. (2010) measured PBB in serum collected in 1987–1988 from participants in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study and compared the 90 controls who remained free of diabetes with 90 cases diagnosed with diabetes many years later in 2005–2006 and found a significant 3-fold increased risk.

However, the majority of the studies were retrospective cohorts and case-control studies or cross-sectional. Temporal relationships, by definition, were not possible to determine in cross-sectional studies and reverse causality, in which certain diseases such as diabetes may increase accumulation or inhibit the clearance of these chemicals could not be ruled out (Lee et al., 2010).

4.3. Strength of the association

Although weak associations between BFR exposure and alterations in thyroid function have been reported, stronger associations have been reported for diabetes (Lee et al., 2010), cancer, neurodevelopmental and reproductive health effects. In most instances, these associations remained significant when confounding variables were considered. The limited number of studies and small sample sizes (only 11 studies with sample size >450 persons), however, are an important concern.

4.4. Consistency of the association

Although a few studies reported significant effects for their study endpoints, consistency of associations was difficult to evaluate due to differing exposure levels, health parameters and exposure and outcome measurements. It is also notable that European countries, such as Sweden, Norway, and Spain had lower exposure levels than in the USA making it difficult to compare study outcomes from different regions of the world.

BDEs were associated with raised TSH levels in two different and independent study populations (Herbstman et al., 2008; Zota et al., 2011). Zota et al. (2011) found positive associations between TSH and concentrations of lower brominated PBDE congeners although associations with total and free T4 were mostly weak and inconsistent. Similarly, Herbstman et al. (2008) reported that prenatal BDE exposure was positively associated with TSH and negatively with TT4 and free T3 among infants born by spontaneous unassisted vaginal delivery. The observed relationships were consistently in the same direction even though not always individually statistically significant. Three other studies, however, did not find statistically significant associations (Bloom et al., 2008; Chevrier et al., 2011; Eggesbo et al., 2011) while Stapleton et al. (2011) found the opposite, in other words positive associations between BDEs and T4 levels. Although the study by Chevrier et al. (2010) did not find a significant association between BDEs and TT4 they did observe a similar trend to the Stapleton et al. (2011) study with an inverse association between BDEs and TSH as low TSH levels is associated with high T4 levels. Again, differences in exposure matrices, timing of measures of thyroid hormones, PBDE congeners measured and analytical and statistical methods make direct comparisons difficult and hence more studies with appropriate exposure assessment are needed before a definitive conclusion can be made regarding the consistency of the association.

Comparisons of human and animal studies reveal inconsistent results regarding the relationship between thyroid hormones and neurodevelopment. It is important to note that animal studies generally report hypothyroinemic effects of exposure to PBDEs whereas varied effects of PBDE exposure on thyroid function in humans (inhibitory, stimulatory or none) causing both increases and decreases in thyroid hormones and TSH levels have been reported in the literature. Physiological differences between rodent models and humans may explain why animals and humans respond differently to these exposures and rodents may be more susceptible to thyroid hormone disruption following exposure to PBDE. Furthermore, complications of labour and delivery can alter thyroid hormone function in mothers and infants at time of delivery. Herbstman et al. (2008) showed that prenatal BDE exposures were associated with reduced T4 levels among infants born by unassisted vaginal delivery and intrapartum stress related to delivery mode may conceal hormonal effects of PBDEs.

The evidence for carcinogenic effects in humans was inconsistent with studies showing an increasing dose–response relation for ‘digestive system’ cancer risk and lymphoma risk, but not for other sites of cancers, including prostate, lung and larynx, breast, ‘female reproductive system’ or ‘urinary system’ (Hoque et al., 1998). An increased OR of 2.5 (95% CI = 1.02–6.0) was reported for testicular cancer (Hardell et al., 2006). Other studies, however, showed no association with non-Hodgkin lymphoma, testicular cancer or breast cancer (Hardell et al., 2009; Hurley et al.,
2011). For neurobehavioral and developmental disorders, two out of the four included studies reported significant impairment of their specific health parameters in childhood with BFR exposure (Gascon et al., 2011; Herbstman et al., 2010). In particular, Herbstman et al. (2010) found a statistically significant association between children exposed to higher levels of PBDE 47, 99 and 100 in their cord blood and a lower score on mental and physical-developmental tests at ages 12–48 months and 72 months. Although the other two included studies did not show significant associations, it is important to note that the Fitzgerald et al. (2011) study investigated neuropsychological status in adults 55–74 years of age and the Hertz-Picciotto et al. (2011) study was carried out on a small sample of less than 100 children.

4.5. Dose–response relationship

Hoque et al. (1998) found an increasing dose–response relationship for digestive system cancer risk after adjustment for age, family cancer history, cigarette smoking, alcohol drinking, and baseline serum PCB level: OR of 8.23 (95% CI 1.27–53.3) for PBB exposure of 4–20 ppb; 12.3 (95% CI = 0.80–191) for exposures of 21–50 ppb, and 22.9 (95% CI 1.34–392) for PBB exposure levels over 50 ppb. Univariate analysis for PBB level and lymphoma risk also showed a dose–response relation: OR 3.24 (95% CI 0.24–95.9), OR 20.5 (95% CI 1.51–608), and OR 32.6 (95% CI 3.33–861), for the corresponding PBB exposure categories, respectively. However, it is important to note that this study did not observe dose–response relationships for the many other cancer sites included and also found no relationship between baseline serum PCB levels and excess cancer risk for all sites combined.

In addition, a typical linear dose–response pattern is not predicted for many of these chemicals and non-monotonic (non-linear) responses and low-dose effects have typically been associated with compounds with endocrine disrupting effects (Vandenberg et al., 2012). In a study of several POPs, including PBB, POPs showed nonlinear associations with diabetes risk with highest risk observed in the second quartiles suggesting low-dose effects (Lee et al., 2010). This may also explain the different effects observed in some animal studies exposed to high doses and human populations exposed to low doses of these chemicals.

4.6. Consideration of alternative explanations

It is also important to consider that individuals are exposed to a mixture of hormonally active chemicals, often at chronic low doses and that exposure profiles are also affected by diet and migration history. It is therefore difficult to consider a single chemical as a marker of total exposure. Many of these endocrine disrupting chemicals also act additively and the multiple and complex effects of these chemicals are dose-dependent and contextual (Soto, 2010). Studies that accounted for confounding variables still found significant associations between exposure to BFRs and adverse outcomes in exposed populations. Herbstman et al. (2007) found comparatively lower levels of PBDEs in infants of Asian mothers living in Baltimore, USA, and hence adjustment for ethnicity may be of particular importance given its impact on health effects and exposure levels. With regard to PBDEs and thyroid function, there is also the possibility that other unmeasured factors such as iodine status may affect the relationship.

4.7. Assessment of evidence

We used the grading system for assessment of carcinogens developed by the World Cancer Research Fund (WCRF, 1997) as a guideline for evaluation of the level of evidence. We concluded that ‘possible evidence’ exists for a relationship between BFR exposure and alteration of thyroid hormone levels, neurodevelopmental disorders, diabetes and reproductive health, particularly decreased birth weight and longer time to pregnancy and possibly cancer but more well designed research is needed to support these tentative but biologically plausible associations.

This systematic review not only provides an important summary of the literature relevant to the human health effects of BFRs, it highlights research gaps and helps to define priorities for future research, particularly with regard to children’s health.

There are however certain limitations. Firstly, this review may be subject to publication bias because non-significant findings are less likely to be published. Furthermore, only significant estimates are reported in many studies meaning that effects that cannot be validated statistically were not included. Another limitation is that, since individuals cannot be randomly allocated to case groups, the influence of confounding variables cannot be fully evaluated. Different studies controlled for a range of possible confounders including socio-economic status, behavioural risk factors, exposure to other environmental toxicants and ethnicity making comparisons difficult. Furthermore, we cannot exclude that residual confounding or unmeasured potential confounders may still remain and that some of the effect of these chemicals on health may still be explained by confounding. Other unmeasured POPs could also play a role in the development of these diseases as serum concentrations of POPs are highly correlated in the general population (Lee et al., 2010). Isolating health effects to a particular BFR or combination of BFRs in the absence of other exposures is complex making the results of these kinds of studies complex and analytically challenging. Furthermore, the possibility of reverse causation between the health outcomes and BFR levels cannot be discounted in many studies, particularly if exposure was assessed close to the time of diagnosis as certain health outcomes may affect BFR levels. A well-designed large prospective study such as the Michigan Cohort has the added benefit that since exposure was measured closely after the accident and health effects were measured many years after exposure occurred the risk of reverse causality is reduced. Furthermore, since BFR exposure was a result of an accident, exposure levels are more random and less likely to be associated with potential confounders such as diet. Exposure to other POPs such as PCBs was also measured in this cohort enabling the assessment of confounding by other POPs.

It is also difficult to generalise the association between BFRs and health outcomes, as most articles investigated PBDEs or PBB only, and excluded HBCD and TBBPA. We found only one study (Egggesbo et al., 2011) investigating the relationship between HBCD in human breast milk and TSH. Limited available data on TBBPA and HBCD may be due to the slower development of analytical techniques required for determining concentrations of these chemicals meaning that these are not routinely analysed. Improvement in analytical techniques means that examination of health effects and exposure to these chemicals is now improved and will be increasingly undertaken. Therefore, encouragement of further epidemiological studies examining PBDEs and PBB but also TBBPA and HBCD are recommended and would enable a more accurate assessment of the health effects of all BFRs. BFR concentrations were estimated as categorical variables in many selected studies which could lead to loss of power because of reduced variability (Freisie et al., 2010) and most studies required larger sample sizes to observe associations. Thus, continuous measurements in large studies are recommended to overcome this. In addition, many included studies were cross-sectional which by definition cannot prove a temporal relationship between exposure and outcomes. In addition, timing of the sampling is also important to consider as for some health outcomes such as reproductive health effects, levels measured for exposure assessment may not reflect early life
exposure. Large birth cohort studies are needed allowing prospective measurement of the environmental effects of these chemicals including biomonitoring data in order to determine the most vulnerable period or critical window of exposure for biological effects. This will also allow better understanding of exposure–response relationships ensuring adequate adjustment for confounders, assessment of specific chemicals in more detail, and also improve understanding of potential mechanisms of action and gene – BFR interactions in order to explore a causal connection.

Different classes of BFR (e.g. PBB and PBDEs) from populations at differing levels of exposure (e.g. accidental and background exposure) were used in studies, from a combination of blood and breast milk samples, in infants, children, pregnant women, mother–child pairs (investigating association between maternal PBDE concentrations and health outcomes in their children) and adults with occupational exposures. The BDE congeners that were reported and included in the sum PBDE results also differed across studies with 5 BDE congeners, (28, 47, 99, 100 and 153) examined by Chevrier et al. (2010); whereas Stapleton et al. (2011), included 4 BDE congeners (47, 99, 100 and 153). Consistent examination of congeners for the sum of BDE congeners is also recommended for more accurate comparison. These methodological differences together with the limited number of studies presenting effects for similar health outcomes as well as differences in exposure levels between different populations made it difficult to combine studies in a meta-analysis.

5. Conclusion and recommendations

Although epidemiological data are limited, this overview of the evidence suggests a possible relationship between BFR exposure and serious health consequences, namely cancer, such as digestive system cancers and lymphoma, reproductive health effects, alteration in thyroid function, neurobehavioral and developmental outcomes in children, and diabetes. Ongoing research of the impact of BFR exposure particularly on thyroid function is important given the evidence of its effect on brain development and neurological health (Porterfield, 2000). Relatively little is known about the health effects of chronic low level exposure to these chemicals, particularly among children and there is, consequently, urgent need to provide more information for the evaluation of their potential threat to children’s health. Certainly, consistent monitoring and development of methodology that result in ease of sample collection in children as well as more consistent evaluation of exposure and health effects in children and adults would be necessary. It is recognised that there are challenges in working with children particularly with respect to, obtaining informed consent, sampling and the collection of sufficient sample volume in the case of neonates and infants (Heffernan et al., 2013). The development and evaluation of non-invasive sampling matrices as well as increased collaboration with researchers conducting paediatric research is needed to facilitate BFR monitoring in children.

More stringent regulatory requirements to demonstrate that a chemical does not cause a particular health effect and demonstration of no health effects at chronic low doses should be established. Currently, information on the toxicity of many chemicals is not completely understood, especially the mode of action. Studies on the adverse health impacts of many chemicals are scarce and it is important to investigate the synergistic health effects of combinations of different environmentally relevant concentrations of chemicals. Also the minimum health risk level concentrations of many chemicals still need to be confirmed. It is, however, recognised that chemical management regulations must be based on reasonable evidence, and mandatory chemical testing, and user guidelines should be considered to protect potential users in a pre-market setting (Council on Environmental Health, 2011).

In conclusion, limited epidemiological data, weak and inconsistent associations across studies, lack of comparative and large studies with appropriate exposure assessment in humans and incomplete understanding of biological mechanisms precludes the establishment of a causal relationship when assessing the evidence through conventional epidemiological approaches. However, biologically plausible associations between BFRs and health outcomes, widespread production and use of BFRs, the increasing contamination of the environment, in combination with their persistence and bioaccumulation, and important data gaps regarding elevated exposures in children warrant special consideration of BFRs as emerging risks to health. A precautionary approach towards exposure of both mothers and children seems warranted with long-term monitoring and ongoing surveillance to fully characterise risks to health.

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Appendix A. Supplementary material

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