MATERNAL AND INFANT HEALTH CONSEQUENCES OF POLYBROMINATED DIPHEYNL ETHERS (PBDEs) EXPOSURE IN PREGNANCY

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ABSTRACT

Background: Polybrominated diphenyl ethers (PBDEs) are persistent flame retardants that are found in the environment. Several reports on PBDEs focus on biomonitoring of these chemicals. However, less is understood in terms of PBDE exposure-related adverse effects in vulnerable populations such as mothers and their neonates. Previous toxicology studies indicate that PBDEs display endocrine disrupting properties. This work aimed to investigate the effect of PBDE on adverse pregnancy outcomes and determine an understanding of related maternal toxicity mechanisms with effect biomarkers.

Methods: A systematic review was conducted where articles were collected from four different databases: PubMed, Scopus, Embase and Web of Science. A total of 54 articles that met the inclusion criteria were included from the period of January 2005 and February 2022.

Results: There were 7 studies on maternal outcomes, 29 articles for birth outcomes and 18 on effect biomarkers. There were consistencies in the direction of association between PBDE exposures in pregnancy and risk of gestational diabetes, gestational hypertension, and pre-eclampsia based on the few studies in this review. Maternal PBDE level was implicated in preterm birth and fetal growth restriction. Most studies found a negative trend in correlation with birth weight, birth length and head circumference. BDE-28 was a common congener to be associated in a decrease in birth length. Studies on thyroid hormones were inconsistent but it was observed that BDE-47 was predominantly associated with a decrease in the relationship.

Conclusion: The findings from the systematic review demonstrated consistent evidence of the association between PBDEs and adverse pregnancy health outcomes, while others showed inconsistencies. Differing study qualities may have contributed to these findings. More studies are warranted to validate the findings with larger sample sizes and longitudinal study designs.

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THESIS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

BDE: Polybrominated diphenyl ether (referring to a specific congener)

BW: Birth weight

BL: Birth length

GDM: Gestational diabetes mellitus

GHTN: Gestational hypertension FGR: Fetal growth restriction

HC: Head circumference

PBDEs: Polybrominated diphenyl ethers

POP: Persistent organic pollutants

PTB: Preterm birth

TH: Thyroid hormone

CHAPTER 1: INTRODUCTION

1.1 Background and context

Industrialization has increased the exposure to environmental chemicals for the past several years (Zlatnik, 2016). Environmental chemicals are intentionally synthesized for various applications. For instance, environmental chemicals include phthalates, pesticides, and polychlorinated biphenyls (PCBs). The presence of these chemicals in the environment were once deemed harmless to society because of their day-to-day use, however, upon further research, are reported to be harmful to human health (Erguc et al., 2021). Phthalates have been used to produce over 400 million tons of plastics yearly in the United States and have been associated with reproductive issues (Mesquita et al., 2021). Pesticides have been used to protect animals, humans, and agriculture against pests; however, these chemicals end up contaminating water and food sources and have been associated with cardiotoxicity (El-Nahhal & El-Nahhal, 2021). PCBs are used as a flame retardant and for electrical insulation in electrical equipment (e.g., capacitors, transformers), sealants, coolants and lubricants and have been linked to cancerous and noncancerous effects (Christensen et al., 2021). These environmental chemicals are mainly used in trade and commerce and have easily entered the environment in landfills or marine environments during manufacturing (Darnerud et al., 2008). Hence, exposure to these compounds can occur at any point.

PBDEs are a class of environmental chemicals with relatively poor in-depth toxicity information compared to other types of environmental chemicals such as plasticizers. The toxicology of PBDE is a current topic of interest for toxicologists and researchers in understanding its toxicological effects in vulnerable and nonvulnerable human populations (Jinhui et al., 2017). This environmental chemical is the primary focus of the thesis.

1.2 Polybrominated diphenyl ethers

PBDEs are a family of brominated flame retardants that were introduced in 1970s and been used for several years in various consumer products such as electronics, furniture, textiles, plastics, and construction materials (Taheran et al., 2017; Linares et al., 2015; Trudel et al., 2011). Some specific examples of their application include airplanes, automobiles, computer screens, and mattresses (Trudel et al., 2011).

PBDEs act through a chemically weak and thermally labile carbon-bromine bond. When the carbon-bromine bond is broken, the thermal energy releases bromine radicals that obstruct carbon radicals and decrease the flame, while simultaneously reducing heat and carbon monoxide production (Siddiqi et al., 2003). Since PBDEs are additives and are not chemically bound to the polymers during the manufacturing process, a percentage of these chemicals can be released during the production, use, disposal, and recycling process and enter the environment (Domingo, 2022). These compounds are highly resistant to degradation; therefore, they can be transported over long distances and bioaccumulate in human and animal tissues (Linares et al., 2015).

One of the primary concerns with PBDEs is that they are a group of persistent organic pollutants (POPs) with similar properties to PCBs. PCBs are chemical substances with two halogenated aromatic rings attached together and differ in their degrees of chlorination, while PBDEs differ in their degrees of bromination. PBDEs and PCBS are persistent organic pollutants (POPs) and coexist in the environment. They are both lipophilic and highly bioaccumulative (Lyche et al., 2015). In the literature, both compounds coexist in the environment and have been studied together for their environmental footprints (Lavandier et

al., 2013; Yin et al., 2017). However, PCBs have been more researched in review studies as compared to PBDE in terms of their effect during pregnancy. Review articles have either included PCBs in association with other environmental pollutants (El Majidi et al., 2014; Tsai et al., 2017) or on its own (Berghuis & Roze, 2019; El Majidi et al., 2014) in regard to health outcomes during pregnancy.

There are 209 compounds called congeners of PBDEs that exist and are categorized under 10 different classes (ATSDR, 2017; Environment Canada, 2006; Environment Canada,

2013). These include:

- monobromodiphenyl ether (monoBDE)
- dibromodiphenyl ether (diBDE)
- tribromodiphenyl ether (triBDE)
- tetrabromodiphenyl ether (tetraBDE)
- pentabromodiphenyl ether (pentaBDE)
- hexabromodiphenyl ether (hexaBDE)
- heptabromodiphenyl ether (heptaBDE)
- octabromodiphenyl ether (octaBDE)
- nonabromodiphenyl ether (nonaBDE)
- decabromodiphenyl ether (decaBDE)

Each class of PBDEs have the same base structure with different number of bromine atoms. For instance, tetrabromodiphenyl ether has three bromine atoms ($C_{12}H_6Br_4O$), whereas hexaboromodiphenyl ether has six ($C_{12}H_4Br_6O$) (Environment Canada, 2013; United States Environmental Protection Agency, 2009; ATSDR, 2017). Differences in physicochemical properties of the classes such as molecular mass (e.g., decaBDE is heavier than triBDE), affects their toxicity and persistence in the environment (Environment Canada, 2011). Congeners are compounds that fall under each class and have the same number and types of atoms but differ only in the position of the bromine atoms on the aromatic rings, hence they are isomers (ATSDR, 2017). Under pentaBDE, for instance, the

primary congeners that make up this class include BDE-47, BDE-99, BDE-100. Under octaBDE, BDE-183 is the major component (over 40%) while under decaBDE, decabromodiphenyl ether, BDE-209, is the prominent component (>97%) of the mixture (Yuan et al., 2016; Trudel et al., 2011; Kefeni et al, 2011).

PentaBDE ($C_{12}H_6Br_5O$), OctaBDE ($C_{12}H_2Br_8O$) and DecaBDE ($C_{12}Br_{10}O$) are the most widely used commercial mixtures in commercial formulation productions worldwide and DecaBDE account for approximately 83% of the total PBDE production (Linares et al., 2015; Trudel et al., 2011; Environmental Canada, 2016). Commercial mixtures are unique because they are made of more than one of the ten classes of PBDEs (Environmental Canada, 2013). In 2001 alone, more than 50 kilo tonnes were utilized of these three classes (Trudel et al., 2011). In the USA and Canada alone, from 1970 to until 2020, it was estimated that about 46000, 25000 and 380000 tons of commercial PentaBDE, OctaBDE and DecaBDE have been used and will continue to be consumed (Abbasi et al., 2015).

1.3 PBDEs regulations in Canada and in other countries

PBDEs are imported into Canada as raw materials such as chemical formulations, resins, polymers, or substrates. Furthermore, PBDEs are also imported as semi-finished materials or as finished products. They are sold as three different forms of mixtures of PentaBDE, OctaBDE, and DecaBDE. These mixtures have been reviewed by Health Canada and Environment and Climate Change Canada and are found in the "*Risk Management Strategy for Polybrominated Diphenyl Ethers (PBDEs)"* document (Government of Canada, 2018; Government of Canada, 2020).

Over the past years, the regulatory bodies have become more stringent for the use of PBDEs. PBDEs were initially placed under the *Canadian Environmental Protection Act (CEPA) 1999* as of December 2006. More information is found under the *Prohibition of Certain Toxic Substances Regulations, 2016* (Government of Canada, 2021). In 2008, the Government of Canada added regulations to prohibit the manufacture, use, sale, offer for sale and import of all 7 classes of congeners and commercial mixtures, polymers, and resins of pure PBDE products (Government of Canada, 2020). Further amendments have prohibited the manufacture, use, sale, offer for sale and import of substances that contain PBDE as of December 23, 2016 (Government of Canada, 2020); however, there are some exemptions. Regulations towards the exemptions, permits and laboratory uses include but are not limited to (Government of Canada, 2017):

Exemptions

- The import, manufacture, use, sale and offer for sale of PBDEs or a product containing them, if PBDEs are incidentally present

Permits

- A permit is required to continue importing DecaBDE and/or products containing it once the regulations come into force

Laboratory Uses

- The prohibition does not apply to listed toxic substances, or to any products containing PBDEs, that are to be used in a laboratory for analysis, in scientific research or as a laboratory analytical standard

In the European Union (EU), the Restriction of Hazardous Substances (RoHS) Directive came into effect as of 2003 which required that new electricals and electronic equipment on the market be PBDE free. The mixtures of PBDE that were targeted in this initiative were PentaBDE, OctaBDE, and DecaBDE. For DecaBDE, these substances were disregarded if their quantities exceeded the maximum prescribed concentrations. In 2004, the EU limited the use and import of products that contained more than 0.1% Penta- or Octabromo diphenyl ethers. Sweden (an EU member state) and Norway (a non-member state) had banned the use of DecaBDE (Trudel et al., 2011). In Germany, the industrial manufacturers have voluntarily agreed to phase out PBDE in 1986. In 1993, Germany placed official limits on PBDE use in plastic production under its Dioxin Ordinance to protect workers' health (Fromme et al., 2009).

In 2003, California was the first state in the United States (US) to pass a bill to ban PBDE and phase out the use of penta- and octaBDE in 2006 (Fromme et al., 2009; Siddiqui et al., 2003). DecaBDE had been used for a while after PentaBDE and OctaBDE were restricted in most states of the US at the end of 2004; however, DecaBDE was voluntarily phased out later in the US towards the end of 2013 (National Collaborating Centre for Environmental Health, 2013; Trudel et al., 2011).

1.4 Sources of Exposure

PBDEs are emitted into the environment from production facilities, e-waste dismantling sites and waste burning (Jiang et al., 2019). According to Wang et al. ‘s (2021) study, five different environmental medias (air, dust, soil, food, water) were identified to be contaminated with PBDE (Wang et al., 2021). Among these five medias, air particles and indoor dust have the highest PBDE concentration (Genuis et al., 2017; Ghimire et al., 2019; Wang et al., 2021).

PBDEs are typically man-made synthetic chemicals, but recent evidence suggests that they can also come from oxygen-producing marine organisms (Alonso et al., 2014). A natural source of PBDE called methoxylated-PBDE (MeO-PBDE) is found in marine top predator tissues (2′-MeO-BDE-68 and 6-MeO-BDE-47) (Alonso et al., 2014). It is hypothesized that that congener 2′-MeO-BDE-68 is synthesized mainly by sponges (e.g., Dysidea herbacea, D. fragilis, Phyllospongia foliascens and Ephydatia fluviatilis) or associated organisms, whereas 6-MeOBDE-47 is produced by algae or associated organisms (Alonso et al., 2014; Vetter, 2006). Marine wildlife has also been seen to have depositions of PBDE (de Wit et al., 2010). In Canada, there are higher trends of PBDE concentrations biomagnifying in arctic environments (de Wit et al., 2010). In remote areas such as Northern Arctic regions, Canadian ringed seals blubber (Phoca hispida), belugas and minke whales (Balænoptera acutorostrata) had high concentrations of PBDE in their tissue (Houde et al., 2017; Simond et al., 2017). In a review by Watanabe et al. (2003), PBDEs were found in certain species of sprat/herring/salmon from the Baltic Sea and zooplankton/small herring/large herring/salmon from the Atlantic Ocean. In Montreal, Herring gulls (Larus argentatus) and Ring-billed gulls (Larus delawarensis) that forage in

landfills have been found to have PBDE contamination (Lapointe et al., 2020; Sorais et al., 2021). Bird eggs have been biomonitored for BDE-47 and BDE99 in starling bird eggs (Eens et al., 2013). According to Sorais et al.'s (2021) study, ring-billed gull species had the highest concentration of PBDE in their liver.

PBDEs can also be found in marine and water sediments (Wu et al., 2019). In Canada, water bodies such as Lake Ontario, Lake Michigan and Lake Huron have had drastic increases of PBDE concentrations from 1981 to 2000 from 4.7 to 400.5 µg/kg ww at Lake Ontario, 7.6 to 541.5 µg/kg ww at Lake Huron, and 8.3 to 927.3 µg/kg ww at Lake Michigan. The increases were primarily due to tetra- and pentaBDE congeners as compared to hexaBDEs and heptaBDEs (Environment Canada, 2013). In Europe, the Baltic Sea have been reported to contain various concentrations of PBDE in sediments, algae, and marine species (Dabrowska et al., 2017; Lindqvist & Gustafsson, 2021).

Dietary food of animal origin such as meat, fish and eggs may contain PBDE (Shelagh et al., 2017). Many Canadian fish species have shown contamination (Crimmins et al., 2012). One study examined eighteen species of fish in Canada with 17 congeners of PBDE and found that all fishes had some level of exposure. The highest ∑PBDE levels (27-71ng/g) was shown in the bottom dwelling Common Carp and White Sucker (Gandhi et al., 2017). From a review study, poultry including meat and fish seemed to have the highest PBDE levels as compared to dairy and plant-based foods (Boucher et al., 2018). Human exposure to PBDEs through air, dust, soil, food, and water consumption is an underlying concern.

1.5 Routes of Exposure

Routes of human exposure include inhalation of soil or indoor dust residues, ingestion of soil, food and breast milk, and hand-to-mouth contact with indoor surfaces of organic films (Linare et al., 2015; Trudel et al., 2011). Linares et al.'s (2015) review found that significant amounts of global PBDE pollution occurred in household dust. Compared to European and Asian countries, Canada and the USA had a 100x greater magnitude where the congeners BDE47 and BDE99 had always remained at higher concentrations in indoor dust and air environments than in human tissue. Sahlström et al. (2014) identified that infants and toddlers are at higher risk of exposure to PBDE through hand-to-mouth contact from surrounding dust in the environment and maternal milk. PBDEs are found in a higher concentration in breast milk in the US as compared to Asia and Europe and the trend of exposure in breast milk was identified to be increasing over time (Fängström et al. 2005; Zhang et al., 2011). As compared to adults, toddlers posed a greater body burden of PBDE by three- to ninefold (Linares et al., 2014). The higher PBDE exposure in the USA as compared to UK and European countries is predicted to have occurred because of stricter fire prevention regulations and greater consumer products containing PBDEs (Trudel et al., 2011). The high persistence of PBDE in breast milk may be because PBDE is highly lipophilic and hence has a greater affinity to remain in the high fat content of breast milk (Gascon et al., 2012). Younger children and infants are still developing and have a lower metabolism rate as compared to adults (Landrigan & Goldman, 2011); this may also be the reason why the elimination of PBDE from the body would undoubtedly be less.

Miriam Diamond, an environmental chemist at the University of Toronto Geography Department, identified that PBDEs contamination from dermal contact may be through touching

household items. They identified that minuscule oil droplets travel into the air in homes from activities such as cooking and can deposit on almost any household surface to produce a thin, sticky organic film that can trap PBDE. It was documented that the levels of PBDEs in films on indoor windows were up to 20 times greater than similar films on the outside of those windows (Betts et al., 2008).

1.6 Toxicology

The toxicology of PBDEs is poorly understood (Taheran et al., 2017). It is estimated that PBDEs have a biodegradable rate of 1-12 years in human fatty tissue (Oulhote et al., 2016). The congeners heptaBDE, octaBDE, nonaBDE and decaBDE may break down into lower brominated PBDE congeners such as tetraBDE, pentaBDE, or hexaBDE (Government of Canada, 2020). Environment Canada (2006) and the United States Environmental Protection Agency (2009) have reported that lower brominated PBDEs have higher volatility; hence, they can easily travel in the atmosphere (Watanabe and Sakai, 2003). E-waste reclamation sites in Bangkok, Thailand found differences in the congener patterns in ambient air particles (PM) with lower brominated PBDEs being more prevalent in nearby off-site samples as compared to the PM collected at the e-waste site (Ghimire et al., 2019). The findings from this study indicated that a debromination of PBDEs to congeners such as tri-BDEs and tetra-BDEs during the reclamation process was easily translocated from treated materials to ambient air PM (Ghimire et al., 2019).

Lower brominated PBDE congeners appear to be more easily transmissible from the mother's placenta to the infant as compared to the higher brominated PBDEs which remain in the placenta as identified in Zhao et al.'s (2013) study in the first trimester with mothers that underwent surgical abortion. For example, significantly higher ratios of BDE28, BDE99, and

BDE47 (pentaPBDEs) in aborted fetus: maternal blood and fetus:placenta were observed relative to BDE197, BDE209, and BDE153 (hexa- and deca-PBDE) which is instead found to be higher in aborted placenta: maternal blood ratios (Zhao et al., 2013). It is known that lower brominated PBDEs are easily transferred to the bloodstream ATDSR (2017).

1.6.1 Biomonitoring

Biomonitoring data on environmental pollutant levels is used for assessing human exposure to harmful chemicals in the population (Li et al., 2020). The Canadian Health Measures Survey (CHMS) was developed with the purpose of studying the exposure to environmental chemicals, including PBDEs, in the Canadian population aged 6–79 years (Government of Canada, 2021; Statistics Canada, 2006). The CHMS initiative provides detailed information on the sources of chemical exposure, the concentration of the substances, and the change in biological systems in the Canadian population (Government of Canada, 2021).

Understanding the body burden of chemicals and/or their metabolites can be useful when it comes to analysing the health risk associated with these exposures (Louro et al., 2019). Based on where these environmental chemicals can occupy in the body (e.g., blood or adipose tissue), human biomonitoring can be an effective tool for measuring suspectable endocrine disrupting chemicals (Faniband et al., 2014) and can be deleterious for the reproductive system among others.

1.6.2 PBDEs as endocrine disruptors

There are some environmental chemicals identified as endocrine disrupting chemicals (EDCs) which are synthetic exogenous chemicals or a mixture of chemicals that can interfere with the endocrine system (e.g., thyroid function). The endocrine system plays a critical role in all vertebrates by regulating metabolism, development, reproduction, and behavior. EDCs can interact with the endocrine receptors and disrupt or alter natural hormone synthesis and breakdown which occur through a series of mechanisms resulting in "false", inadequate or abnormal hormonal signals that can increase or inhibit normal endocrine function which can be deleterious for the reproductive system among others (Street et al., 2018).

PBDEs may behave as EDCs since they may be potential competitors for the binding sites of hormones (Lavandier et al., 2013). For example, PBDEs are structurally similar to thyroxine and in animal studies, they have been shown to have a strong affinity to bind to transport proteins that circulates thyroxine throughout the pregnancy period (See Figure 1) (Chevrier et al., 2010; Walter et al., 2017). Additionally, BDE-99 and BDE-47 were both involved in upregulating estrogen receptors in the ovaries or uterus of rats (Ceccatelli et al., 2006; Karpeta et al., 2014). The effect of PBDEs on hormonal changes demonstrates the importance that PBDEs may have on reproduction which leads to the importance of investigating its effects during pregnancy (see section 1.10.2).

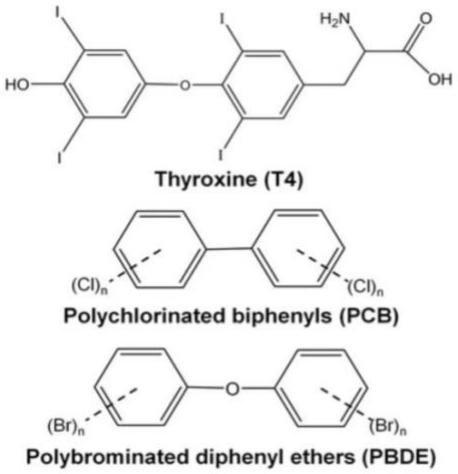

Figure 1: Comparison between the chemical structure of the thyroxine (T4), PCB & PBDE

Retrieved from Walter, K. M., Lin, Y., Kass, P. H., & Puschner, B. (2017). Association of Polybrominated Diphenyl Ethers (PBDEs) and Polychlorinated Biphenyls (PCBs) with Hyperthyroidism in Domestic Felines, Sentinels for Thyroid Hormone Disruption. BMC Veterinary Research, 13, 120. https://doi.org/10.1186/s12917-017-1031-6. No changes were made to this figure.

EDCs can harm not only the exposed specie but also future generations and their offspring through a process called transgenerational inheritance (Barouki et al., 2012). This effect demonstrates the developmental origins of health and disease, a new paradigm for a noncommunicable disease (DOHaD). Worldwide, industrial chemicals acting as neurotoxicant EDCs in the developing brain have been linked to an increase in neurodevelopmental disabilities such as autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), infant/child depression, social disorders, and dyslexia (Street et al., 2018). Thousands of animal studies show direct causal relationships between in-utero chemical exposure and disease outcomes, and in some cases, their negative effects have been shown to be passed down to subsequent generations via transgenerational epigenetic inheritance (Street et al., 2018).

1.7 Exposure of PBDEs during pregnancy

Pregnancy is a critical developmental period for both the mother and developing fetus (Chen ZJ et al., 2013). There is evidence that PBDEs can cross the mother's placenta to fetal circulation (Chen ZJ et al., 2013; Li et al., 2013; Zhao et al., 2013). As mentioned in the last section, exposure to harmful chemicals is believed to be a precursor to adverse health effects in adulthood; however, generational, and transgenerational transmission of diseases are believed to be caused by such exposure to pregnancy (Zota et al., 2018).

Toxicology studies have examined the general effect of PBDE in zebra finch. One study found no effects (e.g., hatching success, chick growth, thyroid hormone levels, or hematological traits) (Winter et al., 2013); however, another study evaluated a mixture containing 22 PCB and 7 PBDE congeners in four generations and found there to be an effect to hypoactive larval behavior and modified gene encoding DNA methyltransferase (dnmt3ba) suggesting interference in DNA methylation pathway involved in neurogenesis in the brain (Horri et al., 2018). Evidence on PBDEs causing multiple generational transmission and its effects is limited as there is insufficient studies.

A healthy immune system is extremely important during pregnancy as several physiological changes occur in the mother's body. This includes weight gain and a rise in blood and plasma volume which can influence the homeostasis of chemical concentrations in the body leading to negative health consequences (Woodruff et al., 2011). During the first trimester, the fetus depends on the mother for nutrient supply. This stage is associated with some controlled inflammatory processes required to maintain the uterine epithelium and remove cellular debris during trophoblast invasion (Park et al., 2022). In the placenta, the

interstitial trophoblast cells interact with uterine natural killer (NK) cells and the extravillous trophoblast and NK cells together are thought to release proteases and cytokines that stimulate dedifferentiation and loss of the smooth muscle cells within the arterial walls. The activation of the NK cells is needed, and genetic studies have revealed that the immune interactions may regulate birth weight across the critical microsomic-macrosomic range (Burton & Jauniaux, 2018). Blastocysts break through the epithelial lining of the uterus to implant; they damage the endometrial tissue to invade; followed by replacing the endothelium of the trophoblast and vascular smooth muscle of the maternal blood vessels to secure an adequate placental-fetal blood supply (Mor et al., 2011). In a placental cell culture study with extra villous trophoblast cell line HTR-8/ Svneo exposed to BDE-47, oxidative stress-mediated activation of inflammatory pathways was seen. As a result of direct stimulation of BDE-47, superoxide production increased, mitochondrial membrane potential decreased, and proinflammatory IL-6 and IL-8 had increased abnormally (Park et al., 2014).

In the second trimester, the fetus grows and develops tremendously fast. The mother, placenta, and fetus share a symbiotic relationship, and the predominant immunological response is to produce an anti-inflammatory state (Mor et al., 2012). In the third trimester, the fetus is completely developed. The proinflammatory phase occurs again to allow for parturition, where immune cells come into the myometrium to promote recovery of an inflammatory process. The proinflammatory status also allows the uterus to contract and expel the baby (Mor et al., 2012).

EDCs are known to negatively cause many reproductive health problems such as infertility, premature ovarian failure, and abnormal sex steroid hormone levels (Patel et al.,

2015). Therefore, at any point in pregnancy, PBDEs could cause interruptions of normal immunological responses and lead to negative health outcomes.

1.8 Maternal health outcomes

Maternal morbidities are a public health concern, and if untreated, it can increase the risk of detrimental health effects for the newborn infant while decreasing the quality of life. Over 50% of women worldwide had died due to hemorrhages, hypertensive disorders, and sepsis between 2003 and 2009 (Geller et al., 2018). Examples of maternal health outcomes that are investigated in this thesis include gestational diabetes (GDM), gestational hypertension (GHTN) and preeclampsia.

GDM is a metabolic disorder diagnosed in pregnancy (Chiefari et al., 2017). Hyperglycemia occurs due to insulin resistance that develops during the second trimester and usually peaks in the third trimester (Chiefari et al., 2017; Soma-Pillay et al., 2016). In most cases after pregnancy, diabetes can progress and if not probably managed, it can be a starting point for early type 2 diabetes and cardiovascular disease (Chiefari et al., 2017). The risk of type 2 diabetes increases seven folds, with a cumulative incidence of 60% at 10 years after GDM diagnosis (Chiefari et al., 2017).

According to the American College of Obstetricians and Gynecologists guidelines, GHTN is defined as a chronically elevated blood pressure that occurs at around 20 weeks of gestation with a systolic blood pressure of >140mmHg and/or diastolic blood pressure of >90 mmHg on two occasions of 4 hours apart (Wisner et al., 2019). A severely high systolic blood pressure of ≥ 160 mmHg and/or diastolic blood pressure of ≥ 110 mmHg, is

considered as preeclampsia. Preeclampsia presents itself with either proteinuria (300 mg or more per 24-hour period) or conditions including pulmonary edema, cerebrovascular disturbances, or signs of kidney failure (Wisner et al., 2019; Maheu-cadotte & Marc-André, 2019). If unmanaged, preeclampsia can progress to eclampsia, which results in the onset of seizures and requires caesarean section. Eclampsia can be dangerous with mortality rates estimated at up to 1.8% in developed countries and up to 15% in developing countries (Maheu-cadotte & MarcAndré, 2019).

1.9 Infant health outcome

Several anthropogenic measures are commonly used by clinicians to measure fetal size and development and determine the health status of newborns such as birth weight (BW), birth length (BL), head circumference (HC), preterm birth (PTB), large for gestational age (LGA), small for gestational age (SGA), fetal growth restriction (FGR), and Apgar score (Azhar et al., 2013; Casadei & Kiel, 2021; Qaiser & Omair, 2016).

HC, BW, and BL are the prime indicators of fetal growth and development (Cabrera-Rodriguez et al., 2019; Casadei & Kiel, 2021; Krishna et al., 2019). A small HC that is more than 2 standard deviations below the mean is called microcephaly and has been associated with poorer cognitive abilities (Kirkegaard et al., 2020). Previously, environmental pollutants studies such as phthalates and parabens, have noted a correlation with a small HC in infants (Bloom et al., 2021; Vrijens).

Infants that are born with very low birth weight (VLBW) have significantly lower intelligence quotient (IQ) in childhood and poor cognitive functioning later in life

(Krishna et al., 2019; Kirkegaard, 2020; Peltier et al, 2015). Additionally, having a VLBW increases the risk of cardiovascular disease later on in life (Alexander et al., 2015). VLBW infants were associated with having a poor microbiome composition (Groer et al., 2015; Yee et al., 2019). Infants with VLBW were born with less microbiome composition from the maternal gut which is the protective barrier and foundation for an infant's gut composition (Yee et al., 2019). A poor microbiome composition can be implicated with several negative health outcomes such as diabetes, obesity, and depression (Limbana & Eskander, 2020; Singer-Englar, 2019). In animal studies, PBDEs has been associated with lower birth weight (<2500g), although the associations have been inconsistent (Du et al., 2015). A meta-analysis study on female Sprague-Dawley rats exposed to decaBDE from five weeks of age to delivery found a negative correlation with birth weight among seven studies (Zhao et al., 2017). Other studies have found no correlation between PBDE and no birth weight as well (Kim et al., 2009).

PTB occurs when the fetus is born at less than 37 weeks of gestational age and has been associated with having a low IQ in childhood as well as with higher blood pressure, increased insulin resistance and reduced kidney volumes which all relate to the increased risk of cardiovascular disease (WHO, 2018; Alexander et al., 2015; Campisi et al., 2019; Hart et al, 2004; Kirkegaard, 2020).

LGA babies are born with a birth weight above the 90th percentile for gestational age. They are more likely to experience brachial plexus injury, have a lower Apgar score and other birth traumas (Cabrera-Rodriguez et al., 2019; Khambalia et al., 2017). SGA, as defined as being below the 10th percentile in birth weight for their gestational age have been

associated to similar negative implications as LBW and PTB infants such developing lower IQ, having a higher risk of cardiovascular disease and type 2 diabetes (Kramer et al. 2001; Campisi et al., 2019; Cabrera-Rodriguez et al., 2019).

FGR is a multifaceted disease that can occur with changes in maternal, placental, or fetal conditions (Burton and Jauniaux, 2018; Audette & Kingdom et al., 2018; Zheng et al., 2016). FGR is most often characterized as an estimated fetal weight that is less than the 10th percentile for gestational age (American College of Obstetricians and Gynecologists [ACOG], 2019). It is usually a manifestation of inadequate trophoblast invasion and impaired uterine-placental perfusion which makes an infant with FGR different from one with SGA alone (Figueras et al., 2017; Mifsud and Sebire, 2014; Reynolds et al., 2006). Placental dysfunction prevents optimal growth and development due to inadequate nutrient and oxygen exchange in the maternal-fetal circulation (Nardozza et al., 2017). Fetuses with FGR present a greater risk of perinatal morbidity and mortality as well as long-term health defects including impaired neurological and cognitive development and cardiovascular or endocrine diseases in adulthood (ACOG, 2019).

According to Osuchukwu & Reed (2021), babies that are born SGA or with FGR are likely to have a smaller birth length which can result in negative health complications such as poor cognition and language and motor scores (Lee et al., 2017). Additionally, having smaller upper leg extremities have been linked to metabolic syndrome (Pryzbek & Liu, 2016; Liu et al., 2014).

To assess the health status immediately after birth, Apgar score is typically used which is dependent on the measures of five factors of the heart rate, respiratory effort, muscle tone, reflex

irritability, and colour (American Academy of Pediatrics, 2015; Cnattingius et al., 2017). A low Apgar score indicates poor cognition (Odd et al., 2008).

1.10 Biomarkers

Biomarkers from biological matrices can inform us on the susceptibility on the mammal based on the measure of exposure or biological effects (Lowry, 1995; Aronson et al, 2017; Benford et al. 2000). There are different kinds of biomarkers that can be measured in different biological matrices (Aronson et al, 2017; Bowers & McCullough, 2017; Linkov et al., 2009). As clinical endpoints, biomarkers can be used for disease screening, diagnosis, and characterization. They can be prognostic indicators for disease, which are essential for health practitioners in developing individualized therapeutic interventions.

1.10.1 Exposure biomarkers

An exposure biomarker is an endogenous chemical specie that is measured and provides an objective assessment of a chemical exposure. The exposure biomarker in this thesis are PBDEs.

1.10.2 Effect biomarkers

An effect biomarker is a biological molecule that indicates a change to some biological process in the body in response to chemical exposures. Biomarkers of effect can assist in understanding possible intermediate mechanisms related to PBDE exposure linked maternal and birth outcomes (Benford et al. 2000). The effect biomarkers that were of interest included thyroid hormone, reproductive hormones, inflammatory biomarkers, vascular effect

markers, tissue repair and remodelling biomarkers, cell proliferation and growth markers and oxidative stress markers.

1.10.2.1 Thyroid Hormones

Thyroid hormone (TH) is essential in the growth, metabolism, and brain development, especially during the first trimester before mid-gestation (12-22 weeks of gestation) of pregnancy. The human fetus is dependent extensively on maternal THs for early cortical neurogenesis (from week 5–20 of gestation), neuronal migration and early phases of maturation (axonogenesis and dendrogenesis). Harmful effects of abnormal TH levels include pre-eclampsia, low birth weight and premature birth (Silva et al., 2018; Derakhshan et al., 2020).

Two essential thyroid hormones are triiodothyronine (T3) and thyroxine (T4) (Soma-Pillay et al., 2016). T4 is a predominant hormone secreted by the thyroid gland and is considered a precursor of T3 or a prohormone, an active and highly potent form with a smaller half-life than T4. Both hormones are important for the placenta, ovarian, and uterus development as indicated by Silva et al. (2018) in Figure 2 below. During the first trimester, the production of thyroxine-binding globulin (TBG) by the liver increases, resulting in slightly increased levels of maternal serum T4 & T3, free T4 and free T3; however, this usually does not result in clinical significance. Generally, serum free T3 and T4 do decrease slightly in the second and third trimesters of pregnancy (Soma-Pillay et al., 2016). Less than 0.1% of the total amount of circulating TH is in its free form, not bound to plasma proteins, and can be transported into cells by specific carrier-mediated mechanisms. When released into the bloodstream, T3 and T4 bind

reversibly to three different transporter proteins: TBG, transthyretin (TTR), and albumin. T4 has a higher affinity for the three proteins (Silva et al., 2018).

PBDEs can cause thyroid disruption in animal studies. One theory is because PBDEs are structurally similar to T4, which typically has a strong affinity to bind to TBP, for instance, transthyretin, involved in circulating T4 throughout pregnancy (Duntas & Stathatos, 2015). *In vitro* studies have demonstrated that PBDEs and their CYP P450–mediated hydroxylated metabolites can compete for binding sites on TBG in serum. A few hydroxylated PBDEs bind to transthyretin in vitro and compete with triiodothyronine binding to human thyroid receptors α and β (Chevrier et al., 2010). In animal studies, PBDEs were seen to affect thyroid regulation by decreasing circulating levels of TH, altering gene expression of the encoding of thyroid-regulating proteins, and reducing the activity of thyroid-regulating enzymes (Stapleton et al., 2011). Decreased thyroid levels have been associated with unusual neuropsychological development in children and adults. The increased thyroid-stimulating hormone has been associated with increased blood pressure and poorer blood lipid profiles, both risk factors for cardiovascular disease and mortality (Miller et al., 2009).

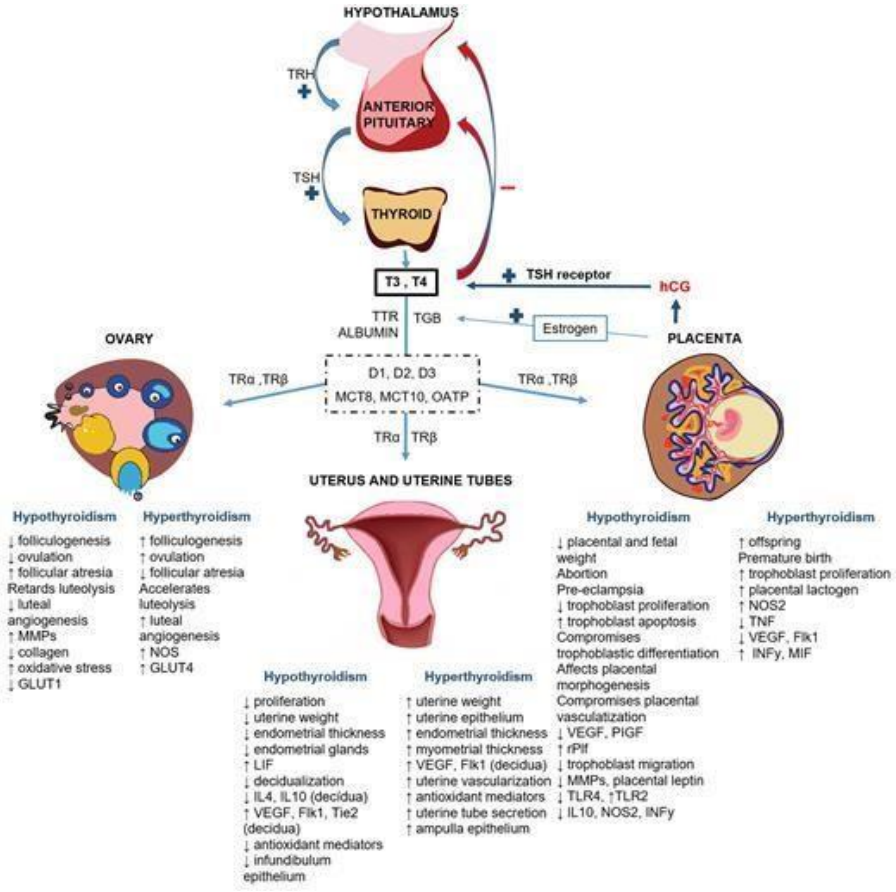

Figure 2: Pathway of thyroid hormone in maternal organs during pregnancy

Retrieved from Silva, J. F., Ocarino, N. M., & Serakides, R. (2018). Thyroid hormones and female reproduction. Biology of reproduction, 99(5), 907–921. https://doi-org.proxy.bib.uottawa.ca/10.1093/biolre/ioy115. No changes were made to this figure.

1.10.2.2 Reproductive Hormones

The regulation of reproductive hormones during pregnancy is essential for the maintenance of good fertility and a healthy fetus. Reproductive hormones include follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), and estradiol (E2).These hormones are essential for spermatogenesis and folliculogenesis (Oduwole et al., 2021). The endometrial cycle, which involves proliferation (during the follicular phase), differentiation (during the luteal phase) and shedding (during menstruation), is the response to the interaction of these hormones (Mihm et al., 2011). FSH individually and in partnership

with LH control the proliferation and maturation of germ cells in women's reproduction and maintenance of menstruation (Kirshenbaum et al., 2021; Mihm et al., 2011). T is also involved in spermatogenesis. LH helps control the production of T by the 23hines cells (Oduwole et al., 2021).

1.10.2.3 Inflammatory Biomarkers

There are various inflammatory biomarkers in the human body that are linked to adverse health events. These include interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-68(IL-8), interferon-gamma (IFN- γ), macrophage inflammatory protein 1-beta (MIP-1β), monocyte chemoattractant protein-1 (MCP-1) and tumour necrosis factor-alpha (TNF-α). Pro-inflammatory cytokine IL-6 is present at the initial stage of inflammation and helps stimulate the synthesis of c-reactive protein (CRP) during acute phases of stress. As a result, this helps in the body protect itself, heal and repair (Del Giudice & Gangestad, 2018). Since during pregnancy, tightly controlled inflammatory processes are active, in line with this, it is reported that IL-6 stimulates prostaglandin production to allow intrauterine contraction and cervical ripening (Torkzahrani et al., 2020). Unfortunately, high levels of IL-6 can be an indication of severe damage. In individuals with PTB, high levels of IL-6 have been associated with preterm premature rupture of the membrane (Akkaya Fırat et al., 2020; Gulati et al., 2012; Massaro et al., 2009). Interestingly, in relation to PBDEs, 5 and 20μM of PBDE have been strongly associated with increased IL-6 levels in a human ovarian granulosa-like tumor cell line (KGN cells) (Lefevre et al., 2016). Furthermore, IL-6 has been shown to stimulate excessive VEGF production, leading to enhanced angiogenesis and increased vascular permeability, which are pathological features of inflammatory lesions identified in synovial tissues of rheumatoid arthritis (Tanaka et al., 2014).

There are four other Interleukin cytokines that are investigated including IL-2, IL-8, IL-10, IL-12. IL-2 causes proinflammation and aids in the proliferation of immunity cells such as B-cells and T-cells. Chronic hypoxia has been associated with pre-eclampsia and poor fetal development. In mice that were postpartum at day 7, chronic hypoxia was associated with reduced IL-2 levels, which are typically related to thymus dysfunction (Zhang et al., 2016). IL-10 is an anti-inflammatory cytokine which helps control acute inflammation in neonatal mice (Zhang et al., 2007). It has been shown to be significantly lower in pre-eclamptic patients as compared to normal patients (Lamma et al., 2021). The progression of pre-eclampsia in relation to low IL-10 levels can cause poor placentation and anti-angiogenesis activation (Lamma et al., 2021).

In the placental explants of PTB infants, PBDEs were also associated with reduced e-coli-stimulated IL-10 production (Peltier et al., 2012). IL-12 has a pro-inflammatory and anti-inflammatory nature (Chang & Radbruch, A, 2007). Increased IL-12 levels were identified in low-birth-weight infants of severely pre-eclamptic women in the third trimester (Cemgil Arikan et al., 2012). In pre-eclamptic rats, increased levels of IL-2 have been associated with decreased placental weight and stimulation of natural killer cells in response to placental ischemia (Cunningham et al., 2018). In contrast to the pro-inflammatory effect, in autoimmune joint disorder patients, the absence of IL-12 exacerbated collagen-induced arthritis (Murphy et al., 2003). IL-8 was higher in severely pre-eclamptic women (Cemgil Arikan et al., 2012). The interaction of other interleukins and biomarkers with immunity cells is described in Zhang & An (2007) paper and includes a conceptual diagram as shown in Figure 3.

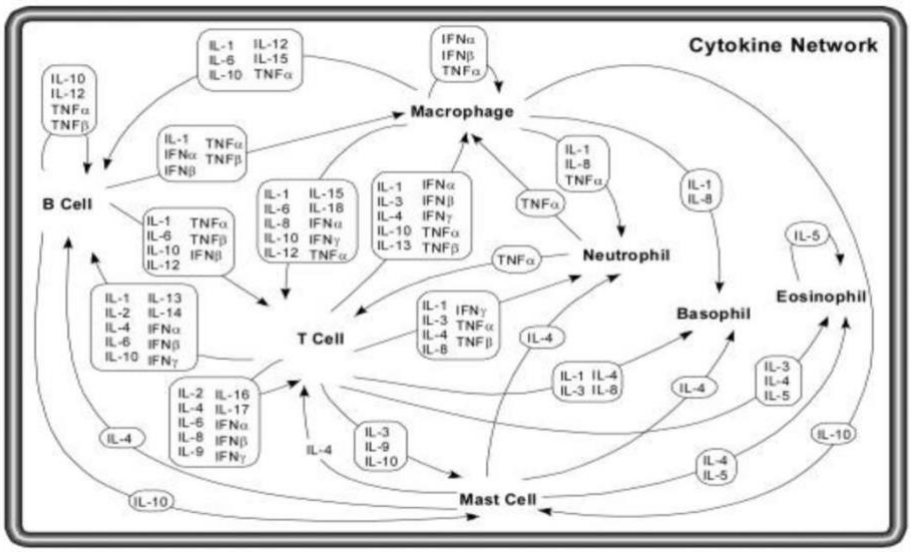

Figure 3: Cytokine interactions with immune cells

Reproduced from Zhang, J. M., & An, J. (2007). Cytokines, inflammation, and pain. International anesthesiology clinics, 45(2), 27–37. https://doi.org/10.1097/AIA.0b013e318034194e. No changes were made to this figure.

IFN-γ is another proinflammatory cytokine secreted by natural killer cells in the maternal endometrium of the uterus (Murphy et al., 2009). According to Liu et al. (2021) and Yang et al. (2014), this cytokine has been expressed at significantly higher concentrations in pre-eclamptic women.

Macrophage inflammatory protein-1 beta (MIP-1β) and monocyte chemoattractant protein-1 (MCP-1) are both called chemokines and are involved in attracting leukocytes, endothelial and epithelial cells during an inflammatory process (Che et al., 2001; Jiang et al., 2008). In addition, both are responsible for monocyte infiltration in the central nervous system (Crisman et al., 1999; Deshmane et al., 2009). MIP-1β and MCP-1 have been highly expressed in rats with stroke brain injuries (Cowell et al., 2002; Jiang et al., 2008; Babcock et al.,2003).

1.10.2.4 Vascular Effect Markers

Vascular effect markers are those molecules found in the vascular system that aid in damage. The placenta is a unique vascular organ surrounded by blood vessels and receives blood from the mother and fetus (Mirbod, 2018). Growth factors have a specific role in aiding the stimulation of cellular growth, differentiation, and tissue repair. Vascular endothelial growth factor (VEGF) helps the fertilized ovum to implant and in vascular development and formation of the placenta during the entire pregnancy period (Ren et al., 2014). Low mRNA VEGF expression can cause inadequate angiogenesis, vasculogenic and placental development. Increased VEGF production has been involved in placental vascularization conditions such as pre-eclampsia, PTB, gestational hypertension and SGA (Andraweera et al., 2012; Galazio et al., 2004). High concentrations of TNF-α are found in preterm birth infants and overstimulation of TNF-α can lead to pregnancy loss, early and severe pre-eclampsia, and recurrent implantation failure syndrome (Alijotas-Reig et al., 2017; Menon et al., 2006). Vascular Cell Adhesion Molecules (VCAM) have an essential role in early placental development and are stimulated by the presence of other cytokines such as TNF-α and IL-1 (Raynor & Parthasarathy, 1997). In pre-eclamptic women, higher VCAM was seen compared to normal pregnant (Chen et al., 2017). In pre-eclamptic patients, endothelial damage occurs and in response, VCAM increases leukocyte-endothelial attachment and activation (Lyall et al., 1994).

C-reactive protein (CRP) is a common acute phase protein implicated in vascular inflammation in diseases such as coronary artery disease. During pregnancy, high levels of CRP have been associated with GDM in the first trimester and PTB in mid-pregnancy (Leipold et al.,

2005). In pre-eclamptic women, high levels of CRP, TNF-α and IL-6 were found, whereas low levels of MMP-2 and MMP-9 were seen (Teran et al., 2001; Chen & Khalil, 2017).

Intracellular cell adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) are considered acute phase proteins that help activate endothelium vascular effects. ICAM allows leukocytes' adhesion to the endothelium (Poniedziałek-Czajkowska et al., 2016). In gestational diabetes, preterm birth and pre-eclampsia, high ICAM and VCAM levels have been detected compared to healthy controls (Li et al., 2020; Poniedziałek-Czajkowska et al., 2016; Takata et al., 2019; Chen & Scholl, 2014; Szarka et al., 2010).

1.10.2.5 Tissue Repair and Remodeling Markers

Tissue repair and remodelling markers and metal metalloproteinases (MMP) are essential for uteroplacental and vascular remodelling. MMP2 is the primary MMP found in the umbilical cord blood (Chen & Khalil, 2017). Lower MMP1, MMP2 and MMP7 expression may impede uterine growth and enhance vasoconstriction, leading to hypertensive symptoms. These are essential risk factors for developing pre-eclampsia (Chen & Khalil, 2017; Li et al., 2017; Sahay et al., 2018). Hypertensive Sprague-Dawley rats have shown increased TNF-α levels, increased vascular and uteroplacental MMP-1 levels and higher collagen deposition, MMP-7 levels during pregnancy. These are typically involved in inadequate tissue remodelling and placental ischemia (Li et al., 2017).

1.10.2.6 Cell Proliferation and Growth Markers

Granulocyte-macrophage colony-stimulating factor (GMSCF) is implicated in cell proliferation and embryo growth progression, development, and implantation. Decreased

GMCSF levels have been linked to miscarriages, FGR, preeclampsia, and preterm delivery (Zhou et al., 2016).

1.10.2.7 Oxidative Stress Marker

Isoprostane (IsoP) is a reliable oxidative stress marker commonly used in pregnancy for individuals with gestational diabetes. It has been seen in higher concentrations in GDM women as compared to normal pregnant women (Kapustin et al., 2020; Palm et al., 2009; Taschereau-Charron et al., 2018).

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CHAPTER 2: RESEARCH QUESTION AND OBJECTIVES

2.1 Problem statement and rationale

The thesis aims to identify the relationship between PBDEs and adverse pregnancy health outcomes. Based on the brief synopsis of the literature, PBDEs are a topic worth investigating. Multiple sources of exposure to PBDEs increase the risk of exposure to a large section of the population. The deposition of higher levels of these products in the body increases the risk of adverse health effects. Biomonitoring data and temporal trends on PBDEs have been well-studied and widely reported. However, our understanding of the impact of PBDE on health in important vulnerable populations such as pregnant women remain limited. Nearly 100% of pregnant women have some level of exposure to PBDEs (Bradman et al., 2007; Meironyté Guvenius et al., 2003). In the US, almost every participant in a recent study had at least 43 different environmental chemicals in their bloodstream which included PBDEs among other pollutants (Zlatnik, 2016). There is evidence of PBDEs in the blood serum or plasma, placental tissue and/or breast milk being able to transfer from the mother to the fetus (Siddiqui et al., 2003; Chao et al., 2007; Choi et al., 2014; Jakobsson et al., 2012). Pregnancy is a critical period for both the mother and the developing fetus and adverse changes in the body can result in detrimental effects. Hence, the rationale for conducting this research is to find additional information on the adverse health effects, especially on pregnant women and neonates exposed in Canada and elsewhere.

2.2 Research Question and Objectives

The central research question is, “What is the association between PBDE exposure and adverse maternal and infant health outcomes?” Secondly, an additional research question that is to be followed is, “Are the exposure of PBDEs associated with biomarkers and can they play an intermediate role to the relationship of PBDE exposure and adverse maternal and infant health outcomes?” The theoretical underpinnings of the exposure to PBDE, their buildup in the body and interference in the normal functioning of the body is described in Figure 4. The different key objectives of this study are derived from the different pathways shown in Figure 4

Specific Research Objectives

1. To determine the relationship between PBDE exposure and ***maternal health outcomes*** during pregnancy.
2. To determine the relationship between PBDE exposure and ***infant health outcomes*** during pregnancy.
3. To determine the relationship between PBDE exposure and ***effect biomarkers*** during pregnancy.
4. To deduce toxicity mechanisms based on PBDE exposures, maternal effect biomarkers and adverse maternal/infant health outcomes with the help of relevant existing scientific information

The above stated objectives are achieved through the following activities:

a) The first objective was to determine relationships between PBDE exposure and maternal health outcome during pregnancy. A systematic review was conducted to find information related to PBDEs association to maternal health outcomes (gestational diabetes, gestational hypertension, and pre-eclampsia) in previous reports. A manuscript from this review has been submitted to a scientific journal for publication.

b) The second objective was to determine relationships between PBDE exposure and infant health outcome during pregnancy. This was achieved from the systematic review by finding information related to PBDEs association to infant health outcomes (birth weight, birth length, head circumference, preterm birth, fetal growth restriction and Apgar score).

c) The third objective was to determine the relationship of PBDEs to biomarkers of effect. This was achieved from the systematic review by finding information related to PBDEs association and biomarkers (thyroid hormones, sex hormones and inflammatory biomarkers).

d) Finally, the fourth objective is achieved through the analysis of the findings of the systematic review and inferences from the literature.

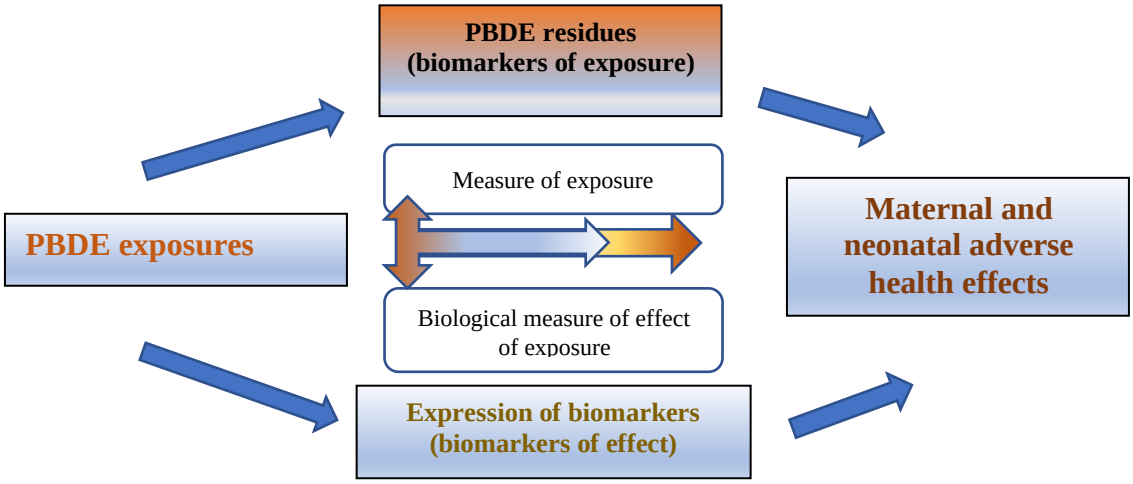

Figure 4: Presumed nature of relationship between exposure and adverse health outcomes in pregnant women and neonates

The data required to find an answer to the research question and the related research objectives were obtained through a systematic review of the literature. The systematic review was conducted by reviewing the worldwide literature on exposure to PBDE during pregnancy and the effect of exposure on the mother and the neonate. In Chapter 3, the methodological steps performed of the systematic review have been covered and Chapter 4 has been devoted to describing the results accrued from the systematic review. The systematic review was used to identify the available evidence and identify research gaps. The guidelines proposed by PRISMA checklist were followed (see Appendix Table 9) (BMJ, 2020; Moher et al., 2009). Chapter 5 focuses on the discussion of the systematic review and Chapter 6 presents the conclusion.

***Note*:** A manuscript based on the review of literature has been prepared and submitted for publication and it is currently under consideration at a journal. The manuscript is titled, "*POLYBROMINATED DIPHENYL ETHERS (PBDEs) AND ADVERSE PREGNANCY OUTCOMES: A SYSTEMATIC REVIEW"*. The list of authors is presented below:

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CHAPTER 3: METHODOLOGY

The preliminary steps used before conducting the systematic review in this Chapter are discussed including the screening and retrieval of articles, the data extraction process, and the quality assessment of articles.

3.1 Systematic review

The purpose of this systematic review was to synthesize the most current knowledge on PBDE and its association to maternal and birth outcomes in addition to accounting for biomarkers for which future research priorities can be identified (Page et al., 2021).

3.1.1 Criteria for Literature Search

The literature search was conducted using Embase (Ovid Embase Classic+Embase), PubMed (https://pubmed.ncbi.nih.gov/), Scopus (www.scopus.com) and Web of Science (Core Collection database via Clarivate) search engines. The following combination of keywords was used in PubMed: (polybrominated diphenyl ether*), (gestational* OR pregnan* OR maternal*), AND (infant* OR newborn* OR neonate*). The resulting combinations of general text keywords and Medical Subject Headings (MeSH) terms were streamlined and developed to adapt in the other databases (see Appendix Tables 1-4). The search strategy was developed with a Health Science librarian. English language and human subject filters were applied. Articles were included if they were published between January 2005 and February 2022. Additional articles were retrieved from hand searching eligible studies that were not captured by the electronic databases.

The details of the search are presented in the PRISMA diagram (Figure 5). The initial literature search from all four databases resulted in a total of 2854 articles and 2 additional hand-picked papers, from the reference list of scientific papers. This resulted in a total of 2856 articles. After removing the duplicates, 1520 articles remained. A total of 105 articles were retained for full-text screening. After reading each article carefully, 51 articles were further excluded based on the criteria outlined in Figure 5 to give a final total of 54 included articles.

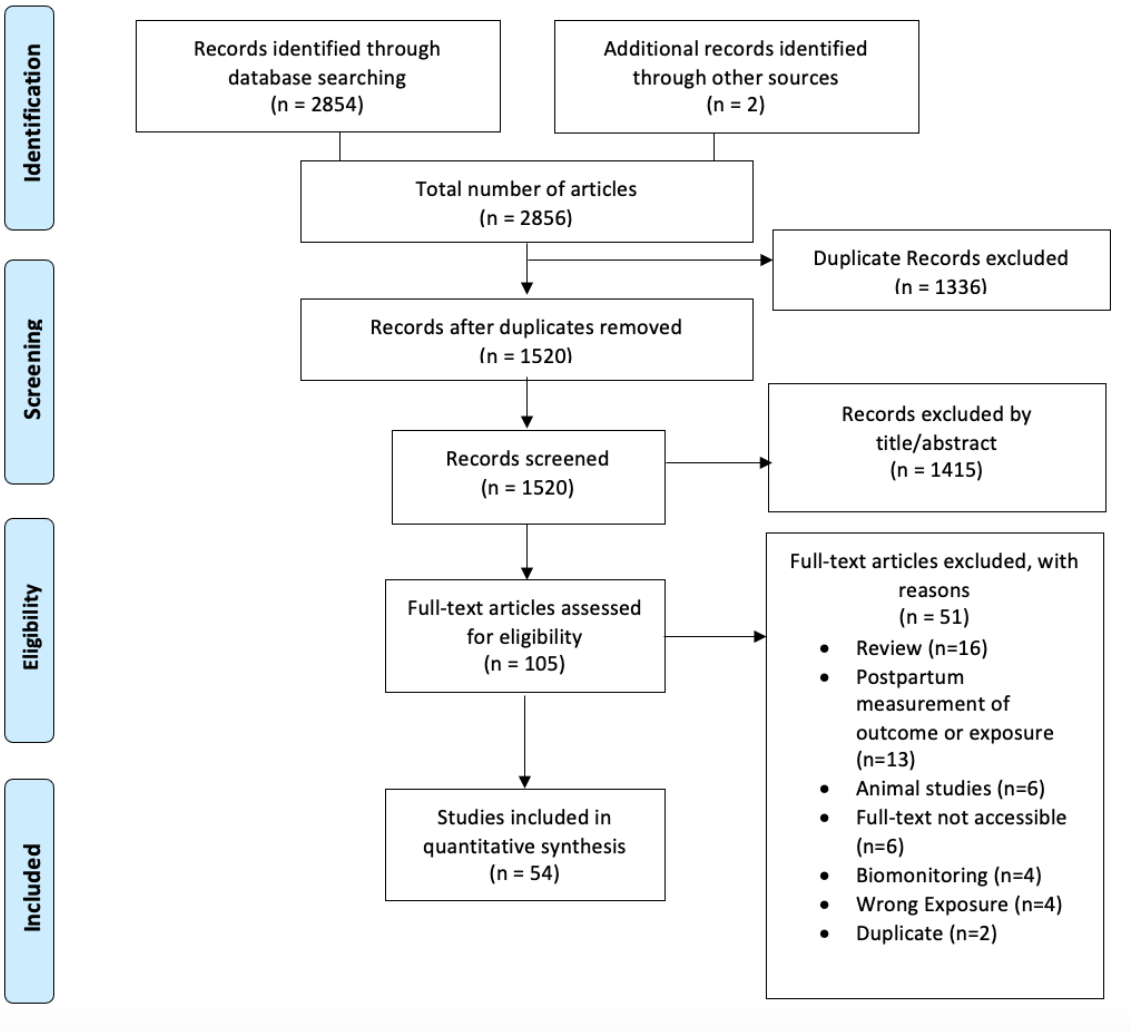

Figure 5: PRISMA flow chart of publications examining PBDEs in relation to adverse pregnancy outcomes

3.1.2 Inclusion/exclusion criteria for the selected articles

Studies were eligible for inclusion if they met the following criteria: (1) PBDE was analyzed as a single congener or a combined mixture of PBDE congeners (ΣPBDE) (2) Exposures were measured during the pregnancy period or at delivery (topics excluded e.g. cryptorchidism); (3) Biomarkers and/or maternal/infant health outcome were measured prenatally or immediately after birth (exposure/outcome measured beyond 1 month postpartum were excluded); (4) Studies considered for the review were with humans (animals or placenta samples were excluded) (5) observational studies were included; (6) Reports were written in English; (7) Full-text articles were available.

3.1.3 Collection and screening of articles

COVIDENCE was used for screening the abstracts and full-text articles. COVIDENCE is a common web-based software used by Cochrane authors for conducting systematic reviews (Cochrane, 2022). It works using a multi-stage process where votes are assigned to articles in terms of "included", "excluded" or "maybe" articles at the title/abstract and full-text level (Kellermeyer and Knight, 2018).

Articles were collected and imported into COVIDENCE. One screener screened all the articles at the title/abstract and full-text level. The second screener verified the ambiguity of studies labelled as "maybe" and decided on whether to include them. They also confirmed whether the inclusion decisions were appropriate (Khangura et al., 2012). The first and second screener reviewed the risk of bias. One reviewer (MB) screened titles and abstracts of all the identified citations and selected

potentially eligible studies. Following the review of the abstract, all relevant full-text articles were assessed by the same reviewer for inclusion and data extraction, and 10% of paper samples were examined by a second independent reviewer (JG). Any discordance was resolved by discussion with the third independent reviewer (PK).

After reviewing all the selected articles, a PRISMA flow diagram was created and shown above in Figure 5. In addition to the flow diagram, the PRISMA has a 27-item checklist created to ensure that the criteria for a review have been properly followed. The checklist is found at the end of the thesis in the Appendix Table 6 (Moher et al., 2009a; Page et al., 2021).

3.1.4 Risk of Bias assessment

The methodological quality of the studies for the risk of bias evaluation was assessed by at least one reviewer using a 7- or 9-point checklist adapted from the Ottawa Newcastle Scale (ONS), as it was the most comprehensive method used to evaluate study quality of nonrandomized studies (Wells et al., 2021). A 7-point checklist was used for cross-sectional studies or 9-point checklist for case-control or cohort studies. An adapted version suitable for cross-sectional studies has been used by Herzog et al. (2013). The role of the scale is to assess a study's design, content, and ease of use in interpreting the results at a meta-analytical level.

The scale is divided into three categories: *the selection of the study groups; the comparability of the groups*; and *the ascertainment of either the exposure or outcome of interest* for case-control or cohort studies (Wells et al., 2021). Each category uses a

"star-system" where a star is added when a study meets the criteria (see Table 5 in the Appendix).

The quality of each study was evaluated based on external and internal validity, completeness of reporting, methodology, confounders, and population demographics. Two authors (MB and JG) reviewed the articles and assigned a numerical value representative of their quality and reported in Table 5 of the Appendix. Study ratings range from 0 to 9 with scores categorized into three groups. Studies with scores between 0-3 were classified as "poor quality" studies, 4–6 were deemed "moderate quality," and 7-9 were identified as "high quality" studies. As no definitions for the cut-off scores for the adapted cross-sectional checklist were mentioned in the search or are universally agreed upon, the cut-off scores were created. Studies with scores between 0-2 were classified as "poor quality" studies, 3–5 were deemed "moderate quality," and 6-7 were "high quality" studies. The results are presented with a "+" sign for each section that met the criteria.

3.1.5 Data Collection and Extraction of Articles

The research question guided the decision on the kind of information to extract from the analysis. Since the focus was to develop a preliminary synthesis of the data and explore relationships, the following format was used (Popay et al., 2006). Standardized data extraction tables were used to illustrate the relevant key information from the published studies including: the author's name, publication year, study design and sample size, country, population characteristics, exposure, outcome, trimester, covariates, study findings and ONS ratings (see Appendix Table 5). Study findings

included statistical measurements such as regression/beta coefficient, odds ratio, or geometric mean, along with the corresponding 95% confidence intervals and/or p-values. After extracting the data, common themes were identified among the studies including the trends in associations, the effects of certain congeners on certain outcomes and common covariates.

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CHAPTER 4: RESULTS

4.1 Results from the systematic review

This literature search yielded a total of 54 articles that met the inclusion criteria. The 54 articles considered for this review included 8 case-control studies, 17 longitudinal cohort studies, and 29 cross-sectional studies (see Table 6-8 in the Appendix). These studies are based on study participants from various countries (e.g., Canada, USA, Australia, UK, China, etc.). Sample sizes ranged from N=20 in cross-sectional studies (Chao et al., 2007) to N=482 in the Hjermitslev et al., (2020) study, with relatively low numbers for case-control studies (e.g., Peltier et al., 2015; Jin et al., 2020) and N=25 to N=2284 subjects for prospective longitudinal cohort studies (Zota et al., 2011; Ouidir et al., 2020).

The 54 studies that contributed to this review reported on the relationship between PBDE exposure measured in various biological matrices and different maternal/infant outcomes and maternal biomarkers during different time points/trimesters during the pregnancy period. Some studies reported on multiple health outcomes of interest therefore were reported more than once in the summary tables (see Table 6-8 in the Appendix).

4.2 Quality Assessment

Based on the ONS criteria for methodological quality, the following results on the quality of the studies were obtained from all of the articles reviewed. Around 19 studies were classified as having high (H) quality (35%), 27 as having moderate (M) quality (50%), and 8 as having low (L) quality (15%). Lower-scoring studies did not

provide clear information on methodology, participant recruitment, self-reported data bias, and did not mention or adjust for confounders in the statistical models used to test the association between PBDE exposure and pregnancy outcomes. Table 5 of the Appendix shows the quality assessment scores for each study. The significance of the risk of bias in terms of the systematic review's strengths and limitations is discussed further in Chapter 5 in the Discussion section.

4.3 Maternal Health Outcomes

Seven articles reported on the association between PBDE exposure and the following adverse maternal outcomes: gestational diabetes mellitus or glycemic indicator, gestational hypertension, and pre-eclampsia (**Table 6**). Three of the studies were case-control studies, three were prospective cohort studies, and one was cross-sectional. All studies adjusted for potential confounders and overall, all studies identified a trend with an increased risk of GDM associated with various maternal PBDE congeners (Eslami et al., 2016, Liu et al., 2018, Mehta et al., 2021; Smarr et al., 2016), except for the inverse association seen by only Smarr et al. (2016) for BDE-47 and GDM who found. Mehta et al. (2021) discovered hydroxylated BDE-47 (5-OHBDE-47) that was linked to a reduction in fasting plasma glucose.

BDE-153 was a common congener found in maternal blood in four studies by Eslami et al. (2016), Liu et al. (2018), Mehta et al. (2021), and Smarr et al. (2016). Liu et al. (2018) had the highest estimated OR risk of 4.04 for GDM (95% CI: 1.92, 8.52) associated with BDE-153. Liu et al. (2018), Rahman et al. (2019), and Smarr et al. (2016) also found a common congener BDE-154 to be associated with increased GDM

risk. Rahman et al. (2019) observed mostly significant positive associations with GDM among women without a family history of type 2 diabetes, whereas a negative association was found among women with a family history of type 2 diabetes. Liu et al. (2018) reported a U-shaped dose-response relationship with BDE-154 where the strongest association with GDM was noticed at the third quartile (OR = 2.58; 95%CI: 1.16, 5.72) concentrations, and a reduced OR in the fourth quartile (OR = 1.70; 95%CI: 0.73, 3.99) versus the reference lowest quartile. Vuong et al. (2021) tested single and multipollutant models and identified a positive association between second trimester BDE-28 and glucose levels at 24 weeks of gestation. Regarding gestational hypertension, Smarr et al. (2016) was the only study conducted that found a nonsignificant increased odds of GHTN associated with BDE-47 and BDE-66.

4.4 Birth outcomes

In this review, 29 articles showed associations between PBDE exposure and adverse birth outcomes such as birth weight, small-for-gestational age (SGA), birth length, head circumference, preterm birth, fetal growth restriction, and Apgar score. Six studies were prospective cohorts, six were case-control and seventeen were cross-sectional. Most studies evaluated PBDE in the matrices of maternal serum, except for 5 that evaluated in breast milk and 9 in the umbilical cord blood (Table 7).

4.4.1 Birth Weight (BW)/Small for Gestational Age (SGA)

Most studies on infant health outcomes were pertaining to birth weight (Table 7). There were appropriately sixteen studies had small sample sizes (N<500). Overall, the majority of the studies observed a significant or non-significant decreased association

with birth weight. For instance, Chao et al. (2007) found maternal breast milk were significantly higher in concentration in the lower birth weight category (≤ 3.05 kg) compared to the higher birth weight (>3.05 kg) category. Furthermore, Eick et al. (2020) and Harley et al. (2011) both found significant negative associations between BDE-47 and BDE-99 exposures with infant birth weight, where Eick et al. (2020) identified a U-shape in their dose-response curve with the mid-tertile showing the most significant decrease in infant birth weight compared to the lowest and the highest tertile. Foster et al. (2011) and Lopez-Espinosa et al. (2015) only found significant negative associations between BDE-99 and birth weight.

Some articles reported on a decreasing trend in infant birth weight (Buck Louis et al., 2018; Chen et al., 2018), whereas others reported no significant associations between these parameters (Hjermitslev et al., 2020; Serme-Gbedo et al. 2016; Stasinska et al., 2014). Buck Louis et al.'s (2018) study stratified for ethnicity and race but yet found a non-significant decrease in birth weight with BDE-28 and BDE-153 exposures.

Similarly, there were studies that reported findings after stratifying for infant sex. For instance, Robledo et al. (2015) showed that female infants exhibited lower birth weights with maternal BDE-28 exposure than male counterparts. On the other hand, Chen et al. (2015) found that maternal BDE-28 exposures were associated with smaller birth weights, only for male infants. Furthermore, Cabrera-Rodriguez et al. (2019), in one model observed a statistically significant negative correlation between BDE-47 and the birth weight and consequently, in another model, a higher odds of SGA, for female infants. Eick et al. (2020) found a stronger correlation with the middle tertile exposure of BDE-47 and birth weight z-scores among females as compared to males.

4.4.2 Birth length (BL)

Nine studies on PBDE exposure and birth length outcome were published (Table 7). The BDE-

28 congener was consistently shown to be negatively associated with birth length. Buck Louis et al.'s (2018) discovered a significant negative correlation between BDE-28 and birth length in infants born to Hispanic women. Meanwhile, Robledo C.A. et al. (2015) study showed that PBDE exposure was significantly negatively associated with a decrease in birth length both in male and female infants. There were two studies that found non-significant negative trends between PBDE exposures and birth length (Harley et al., 2011; Hjermitslev et al., 2020). Others found increased or no association with birth length. Lopez Espinosa et al. (2015) reported on a 2-fold increase in cord blood BDE-47 was associated with statistically significant 2% increase in the mean birth length for females (95% CI: −1.1, 5.0) and 1.4% decrease in mean birth length for males (95% CI: −4.4, 1.6, p-interaction = 0.04).

4.4.3 Head circumference (HC)

Eleven studies looked at the effect of PBDE on infant head circumference (Table 7). Only two studies reported statistically significant, negative correlation between these two parameters. Lopez-Espinosa et al. (2015) found that maternal ΣPBDEs were significantly associated with a decreased head circumference of 1.0cm (β = −2.9%, 95% CI: −5.5, −0.3). Ouidir et al. (2019) found that only maternal BDE-154 exposure showed statistically significant negative association with a −0.34mm decrease in head circumference with respect to the mean (β =−0.34, 95% CI: −0.51

to−0.17). Meanwhile, cord blood BDE-47 was associated with increased HC in female infants on Chen et al.'s (2018) study.

4.4.4 Preterm birth (PTB)

Four studies reported on increased odds for preterm birth (Table 7). For instance, Gao et al. (2016) found that maternal blood BDE-153 levels were associated with a statistically significant increased risk for preterm birth (adjOR=1.05, 95%CI: 1.01, 1.09), Eick et al. (2020) and Peltier et al. (2015) both reported on increased risk of preterm birth with increased maternal BDE-47. Peltier et al. (2015) showed that higher (>1000 pg/ml) maternal plasma BDE-47 exposure at delivery had a greater risk for preterm birth (very high PBDE OR = 5.6, 95% CI: 2.2, 15.2; p <0.001) than women with very low exposure levels (135 pg/ml) (high PBDE OR = 3.8, 95% CI: 1.6, 9.7; p = 0.003). A second study by Peltier et al. (2021) also found that high levels of exposure (≥4.425 ng/mL) to maternal BDE-47, this time in the first trimester, was also associated with an increased odds of developing preterm birth (OR=2.35, 95%CI: 1.31, 4.21).

4.4.5 Fetal growth restriction (FGR)

Two nested case-control studies observed that all PBDE congeners measured in maternal serum and colostrum matrices had significantly increased the odds for fetal growth restriction (Table 7). When the infant cohort was stratified for infant sex in Jin et al.'s, (2020) study, females demonstrated a statistically significant association between maternal BDE-207 and fetal growth restriction in the second trimester (OR = 1.056, 95% CI: 1.002, 1.112). Zhao et al. (2019) reported a log-unit

(10-fold) increase in BDE-206 increased odds of fetal growth restriction by 56.9% in third trimester (OR = 1.569, 95% CI: 1.053, 2.338). The greatest association with FGR was seen with lower-brominated BDEs, BDE-17–190 by 186.0% (95% CI: 1.233, 6.634).

4.4.6 Apgar score

Only three studies mentioned Apgar score associations with PBDE (Table 7). All the studies evaluated PBDEs in the umbilical cord blood. Tan et al. (2020) measured the Apgar score at 1min post-birth and found a positive association with neonatal performance to BDE-47 (estimated $\beta = 0.21$, 95% CI: 0.18-0.24) and BDE-99 (estimated $\beta = 0.15$, 95% CI: 0.05-0.25). On the other hand, Xu et al. (2013) observed no correlation between BDE-100, BDE-154 and Apgar scores. Wu et al. (2010) and Xu et al. (2013) discovered that Apgar scores from Guiyu (PBDE exposed group) were lower than those from Chaoan (control group), with Xu et al. (2013) reporting a significant difference in only female infants.

4.5 Effect Biomarkers

This review found 18 studies on maternal serum, maternal breast milk and cord blood PBDE exposure and its relation to effect biomarker profiles, including changes in thyroid hormones, reproductive hormones, and inflammatory markers (Table 8).

Thyroid hormones were analysed in 16 studies (Table 8). Only eight studies demonstrated a statistically significant decrease in triiodothyronine, free

triiodothyronine, total triiodothyronine (T3/FT3/TT3) and/or thyroxine, free thyroxine, total thyroxine (T4/FT4/TT4) with increased PBDE exposure. According to Lignell et al. (2016), maternal breast milk BDE-153 levels decreased significantly with first trimester maternal TT3 ($\beta = -0.25$, SE = 0.07, $p = 0.001$). Herbstman et al., (2008) found that maternal BDE-153 at delivery was significantly associated with increased odds of low cord blood TT4 and FT4 and Kim et al. (2013) found that BDE47 significantly increased the odds of low maternal TT4 (OR=1.35, 95% CI:1.07, 1.71). Stapleton et al. (2011) in third trimester found that a 2-fold increase in BDE-47 lowered the odds of FT4 by 40% (95% CI: 0.39–0.93) and ΣPBDEs lowered the odds by 49% (95% CI: 0.27–0.97). Also, this group reported that 4´-OH-BDE-47 was inversely associated with TT3 (95% CI: 0.30–0.86).

Only two studies reported on reproductive biomarkers and inflammatory biomarkers in pregnancy with respect to maternal PBDE exposures (Table 8). Gao et al. (2016) found a statistically significant inverse relationship between a log unit increase in BDE-47, BDE-100, and ∑ 5PBDEs and FSH by 1.19 IU/L (95% CI: −1.32, −1.02), 1.17 IU/L (95% CI: −1.36, −1.01), and 1.26 IU/L (95% CI: −1.55, −1.02). Zota et al., (2018) reported a positive association between all maternal PBDEs and inflammatory biomarkers of TNF-a, IL-6, and anti-inflammatory biomarker IL-10, in obese women. In this work, the authors also showed that adoubling of ∑PBDEs level, increased the pro-inflammatory cytokine IL-6 by 15.26% (95% CI:1.24, 31.22) while the inflammatory TNF-a cytokine increased by 3.74% (95% CI: −0.19, 7.82). Exposure to BDE-100 showed a negative association with IL-10 ($\beta = -2.21$, 95% CI: -8.91, 4.99).

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CHAPTER 5: DISCUSSION

5.1 Discussion on Systematic Review

Brominated flame retardants, PBDEs, are used in various consumer products and are known as persistent organic pollutants due to their bioaccumulation and biomagnification properties. Thus, exposure to this class of chemicals leads to environmental and human health concerns. To our knowledge, this is the first systematic review done to gain information on the relationship between PBDE levels in pregnancy and maternal/infant health consequences, along with consideration given to maternal biochemical changes to unravel toxicity mechanisms. The main goal of the systematic review was to explore the relationship that exists between exposure to PBDEs during human pregnancy and adverse health outcomes in studies conducted worldwide. These findings necessitates that the exposure to PBDE is an important public health concern that requires attention.

Thus far, a few review studies have touched upon PBDEs association with health outcomes or thyroid hormones. Kim et al.'s (2014) systematic review synthesized 20 epidemiological articles which addressed PBDEs' relationship to thyroid disorders, diabetes, reproductive health, cancers and neurobehavioral disorders. However, it was not specified to an age group and included both children and adult populations. Similarly, Czerska et al. (2013) conducted a review on PBDEs' association to thyroid hormones in both human and animal populations. PBDEs were included as a subcategory among other pollutants in reviews on health outcomes or thyroid associations (Calsolaro et al., 2017; Pearce & Braverman, 2009; Street & Bernasconi, 2020; Vrijheid et al., 2016).

5.1.1 Impact of PBDEs on maternal health outcomes

In Chapter 4, all the studies conducted for maternal health outcomes suggested an elevated risk of gestational diabetes, gestational hypertension, and pre-eclampsia during pregnancy. It was revealed that the congeners BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154 were commonly involved in gestational diabetes in the studies. Alvarez-Silvares et al.'s (2021) case-control study with placental samples of BDE-99 ($p=0.036$), BDE-100 ($p=0.039$), BDE-153 ($p=0.037$) and BDE-154 ($p=0.031$) were associated with a greater likelihood of developing gestational diabetes at the time of delivery. Mouse dams with perinatal exposure to a PBDE mixture (DE-71) demonstrated elevated fasting blood glucose in female offspring but not their mothers (Kozlova et al., 2020). In a study with six-week-old Sprague-Dawley rats, a daily dose exposure of 14 mg/kg body weight of penta-BDE for four weeks demonstrated lower glucose oxidation and greater insulin resistance in isolated adipocytes (Hoppe & Carey, 2007).

A correlation between PBDEs and diabetes was observed among non-pregnant women and males. Low insulin sensitivity was noted in the sample of 22 obese women and 12 obese males with high adipose tissue levels of PBDE. Additionally, a statistically significant correlation was identified between insulin and BDE-47 and BDE-99 in omental adipose tissues (Helaleh et al., 2018). In a case-control study, higher BDE-47 was associated with a higher prevalence of diabetes among males and females (Zhang et al., 2016). The way PBDE works physiologically and its relation to this phenomenon is still unclear.

In rats, placental disruption of 11B-HSD2 through direct administration of exogenous glucocorticoids to the fetus or through pharmacological inhibition of maternal 11B-HSD2 demonstrated harmful effects. The enzyme, 11B-HSD2 is typically involved in inactivating cortisol to help protect the fetus from exposure to maternal glucocorticoids and furthermore, in controlling hypertension (Alikhani-Koopaei et al., 2004). Zhao et al. (2019) noticed that BDE-17–190 showed a statistically significant positive correlation with DNA methylation of HSD11B2 gene promoter, indicating a possible pathway where PBDE may have underlying effects on 11B-HSD2 promotion and, as a result, may have led to gestational hypertension. Abnormal dysfunction of 11BHSD2 may lead to a series of complications such as increased blood pressure programming, a reduction in nephron number and impaired vascular function and consequently fetal growth restriction leading to health concerns in the offspring later on in life. These are all potential risk factors for cardiovascular disease (Alexander et al., 2015).

In relation to the mitochondria, BDE-47 has demonstrated a disruption to hippocampal mitochondria fusion in PC12 cells involved in neurodevelopment in rats. Also, it has been associated with mitochondrial fragmentation, membrane potential dissipation, ATP loss, and apoptosis activation (Dong et al., 2020). The mitochondria are essential for cellular energy metabolism. A damage to the mitochondria is involved in the mechanisms leading to insulin resistance and decreased oxidative phosphorylation. Although it is not ascertained that mitochondrial dysfunction causes diabetes, there is still a possibility of a link (Kwak et al., 2010). Hence, BDE-47's disruption in the mitochondria may be linked to the establishment diabetes.

5.1.2 Impact of PBDEs on infant health outcomes

Studies that investigated birth outcomes found inconsistent associations between PBDE exposure and birth weight, although most studies found a negative non-significant correlation. BDE-47 was predominately reported to be negatively associated with birth weight (Cabrera-Rodríguez, 2014; Chao et al., 2007; Chen, 2015; Eick, 2020; Harley et al., 2011). In addition to BDE-47, the congeners BDE-99 and BDE-153 were frequently presented and showed similar relationships with infant birth weight. Also, studies were showing significant negative correlations between maternal PBDE levels and infant birth weight after stratification by sex in male or female infants. For instance, Cabrera-Rodríguez et al (2019) found a statistically significant negative correlation between BDE-47 exposure and birth weight in females although there was no association observed in males.

Toxicology studies have identified a similar negative correlation with birth weight. For instance, BDE-47 exposed mice had pups with decreased birth weight (Zhu et al., 2017). *In vitro* exposure of BDE-47 to human first-trimester extravillous trophoblast cells resulted in cytokine release and the generation of cellular reactive oxygen species, with implications for mitochondrial DNA damage (Park et al., 2014). Such findings are relevant for small for gestational age outcomes in infants and are consistent with this review's study findings (Gemma et al., 2006; Weber et al., 2014).

Among the three articles that examined fetal growth restriction and four that looked at preterm birth, all found an increased risk associated with PBDE exposure (Jin et al. 2020a; 2020b; Gao et al., 2016; Eick et al., 2020; Peltier et al., 2015, 2021). All four articles on

maternal PBDE (e.g. BDE-47, -99, -153) identified an increased risk associated with preterm birth (Gao et al., 2016; Eick et al., 2020; Peltier et al., 2015, 2021). PBDEs were linked to cellular necrosis and death in an *in vitro* study using placental explants from mothers undergoing c-sections (Sheller-Miller et al., 2020). BDE-47 and BDE-99 have both been involved to increased cell senescence, inflammation, and induced labour with COX-2 expression in human amnion cells, all of which have been linked to preterm birth (Behnia et al., 2015). BDE-47 increased mRNA gene expression of corticotropin-releasing hormone in the placental cell line JEG-3. Corticotropin-releasing hormone is typically elevated during pregnancy; however, abnormally elevated levels have been observed in preterm birth and fetal growth restriction (Zhu et al., 2017). Placental inflammation, insufficiency and damage are some characteristics linked with preterm birth and fetal growth restriction outcomes (Audette et al., 2018; Gilman-Sachs et al., 2018). It is possible that the underlying effect of PBDEs in causing cellular damage is linked to these negative birth outcomes.

Many studies on birth outcomes had stratified for infant sex; however, results have been inconsistent. Understanding gender implications is vital in epidemiological research as there are differences in the pathophysiology and pharmacokinetics between males and females (Carberry et al., 2010; Fields et al., 2009). Women tend to have a higher percentage of body fat composition than their male counterparts (Karastergiou et al., 2012). Since PBDE is a lipophilic POP that persists in the adipose tissue, it would be worth investigating whether being female would make one more prone to health complications than being a male. Future studies should have similar inclusion/exclusion criteria to enable results to be comparable. A common issue with studies on endocrine-disrupting chemicals when stratifying for sex is that confounders

tend not to be evaluated explicitly according to sex differences (Buckley et al., 2017). Hence results may not produce reliable findings.

Furthermore, in-utero PBDE exposure was linked to shorter infant birth lengths in the majority of studies. One of the PBDE congeners, BDE-28, was shown to be associated with a decreased birth length (Buck Louis et al., 2018; Chen et al., 2015; Robledo et al., 2015). In a recent study by Iszatt et al. (2019), BDE-28 was shown to influence the microbiome diversity of breast-fed infants. Interestingly, gut microbiome changes can impact nutrient absorption, nutrient uptake and gut microbiome compositions which affect neurotransmitters that influence infant growth (Mittal et al., 2017; Scaldaferri et al., 2012). Additionally, Buck Louis et al. (2018) after stratification by ethnicity/race also reached significance where BDE-28 had a significant negative correlation with birth length among Hispanic women only while BDE-153 had a significant negative correlation with birth length only among Black women.

In regard to head circumference, increased maternal PBDE levels were negatively correlated with head circumferences of babies (Miranda et al., 2015; Ouidir 2019). Baby sex-related differences were noted within a few of those studies. However, some studies reported on non-significant negative associations. In general, well-conducted studies reported statistical significance on these associations. As in the studies by Lopez-Espinosa et al. (2015) and Ouidir et al. (2015), these studies included longitudinal prospective study designs, a large number of covariates, a large sample size, and statistical analysis (including tests for effect modification by baby sex, maternal ethnicity/race, sensitivity analysis, and so on) (2019).

Microcephaly can cause neurological impairment if the head circumference is more than two standard deviations below the mean (Harris, 2015). Although these review findings show only minor decreases in head circumference (2SD from the mean), it is possible that long-term exposure to PBDE will have negative consequences. Postnatal studies have revealed neurological issues. Prenatal breast milk BDE-47, -99, and -100 levels, for example, were linked to impaired attention and increased externalizing impulsive behaviours at around 30 months of age (Hoffman et al., 2012). In infants aged 8 to 12 months, cord blood BDE-28, -99, and PBDEs demonstrated delayed adaptive behaviour (Shy et al., 2011). Maternal blood BDE was linked to changes in motor function, cognition, and behaviour in children up to the age of seven (Eskenazi et al. 2013; Roze et al. 2009). Furthermore, as previously stated, PBDE exposure has been linked to higher maternal glucocorticoids, and high levels of maternal glucocorticoids may have a negative impact on fetal brain development and adult HPA axis functioning (Barbazanges, 1996).

The reporting on Apgar score and maternal PBDE levels were scarce, yet there were three studies identified in this review with conflicting findings. Since study quality was rated low for all three studies, more studies are required to investigate this association and draw a conclusion on this relationship.

5.1.3 Impact of PBDEs association to effect biomarkers

In Chapter 4, PBDEs were associated with thyroid, reproductive and sex hormones. Similar to birth weight, the findings on effect biomarkers showed inconsistencies where the studies revealed that PBDEs were mostly related to inconsistent altered thyroid hormone levels. However, BDE-47 was a common congener that showed a decreased correlation with maternal or infant T4. Similar findings were observed in some mechanistic studies (Richardson et al., 2008; Li et al., 2020). For instance, Li et al. (2020) administered oral PBDE-47 at environmentally relevant doses (0.1, 1.0, 10 mg/kg/day) 10 days before and during pregnancy and showed a reduction of serum TH in adult female rats. Moreover, thyroid structure abnormalities and apoptosis were observed. Apoptosis was induced by the triggering stress on the endoplasmic reticulum of the thyroid and by causing lysosomal dysfunction, which led to thyroid toxicity. Other studies found little to no correlation between PBDE and T4 levels. For example, in a study conducted by Andrade et al. (2004) with Sertoli cells of rat testes, they showed varying degrees of correlation where FT4 levels had significantly decreased on postnatal days 14 and 22; however, T4 showed a slight increase in postnatal day 22.

PBDEs have not been previously done. However, one study with garter snakes demonstrated that BDE-47 increased the size of the thyroid glands of the mother and offspring and increased the thyroid follicular height of just the offspring. The study's outcome revealed that the presence of PBDE may have influenced the unusual and high activity of the thyroid gland and structural changes seen during pregnancy (Neuman-Lee et al. 2015).

While many of the studies in the review were on PBDEs' relationship with thyroid hormones, more studies should be conducted with reproductive and sex hormones as they also have a major influence on pregnancy outcomes (Ceccatelli et al., 2006). Gao et al.'s (2016) study from this systematic review on human reproductive hormones identified that PBDEs were associated with a significant decrease in FSH but had no correlation with estrogen, testosterone, or luteinizing hormone. A rat study by Ceccatelli et al. (2006) and Karpeta et al. (2013) with estrogen revealed the opposite, where PBDE has been shown to amplify the effects of estrogen in the body. PBDE has also affected the regulation of estrogen target genes in the uterus. PBDE has also affected the regulation of estrogen target genes in the uterus. Estrogen receptors were seen to be upregulated by low-dose exposure of BDE-99 and BDE-47 (Ceccatelli et al., 2006; Karpeta et al., 2014). BDE-47 was shown to have altered effects on reducing the tertiary follicles and serum estradiol concentrations in the female rate offspring exposed to 700 microg/kg BDE-47. After post-natal day 100, histologic and morphological changes were also characterized in the thyroid glands (Talsness et al., 2008). Similar to Zota et al. (2018) study on sex hormones, a 20 μM PBDE mixture also increased the expression and production of the proinflammatory factor, IL-6, in human KGN cell culture of females (Lefevre et al., 2016). Additionally, BDE-47 was involved in upregulating the gene expression of MMP1 of cytotrophoblast in mid-gestation (Robinson et al., 2019; Varshavsky et al., 2020).

5.1.4 Biomarkers association with adverse health outcomes and their intermediary role

Studying biomarkers with respect to health outcomes is important for understanding the mechanisms of action as it relates to the disease outcome, and there are suggestions that they are promising indicators of health outcomes (Aronson et al., 2017; Beulens et al., 2013).

Biomarkers are necessary for the proper functioning and homeostasis of the body. During pregnancy, the maternal body is dependent on inflammatory and immunological pathways for the successful delivery of a baby (Coussons-Read et al., 2013). They may either behave directly to affect the health outcome or as an intermediate. As an intermediate, a biomarker may have an indirect way of causing the health outcome as a consequence of some environmental exposure, such as PBDE (Mayeux, 2004). The findings from the systematic review are only preliminary. They do not inquire directly on the mechanistic pathway of biomarkers between PBDE exposure and adverse health effects in the human pregnancy population. However, the review does in fact identify that there is an imbalance of hormones correlated with the presence of PBDE exposure.

The link between inflammatory and hormonal imbalance and PBDE congeners is suggested by many *in vitro* studies. As noted earlier, BDE-47 was especially involved in causing inflammation to human first-trimester extra-villous trophoblasts via the mediation of oxygen-reactive species (Park et al., 2014). In minipigs, even in the presence of BDE-47, a change in hepatic UGT and its transporter was noted which is responsible for catabolism of thyroid and low T4 levels. BDE-47 was directly involved in increasing hepatic CAR which is normally involved in thyroid hormone activity which reflect that PBDE have an influence on the modulating the metabolizing pathways of thyroid hormones (Higashi et al., 2014).

According to The Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth (2019), hypothyroidism has been linked to preterm birth. Additionally, hypothyroxemia has been associated with suboptimal neurocognitive conditions in the offspring. Furthermore,

thyroid dysfunction has been linked to unusual fetal and neonatal glucose and lipid metabolism (Molehin et al., 2016). Thyroid is critical for the proper growth and development of the fetus, especially in the first trimester of pregnancy (Soma-Pillay et al., 2016). Inflammatory biomarkers can increase the risk of preterm birth or other adverse pregnancy outcomes (Arita et al., 2018).

Other biomarkers that are essential for pregnancy as mentioned in Chapter 1 have not been discussed in the literature in reference to PBDEs. For instance, there was only one study by Yuan, Meeker & Ferguson's (2017) on PBDEs' relation with oxidative and inflammatory stress biomarkers in adolescent and adult populations in the US looking at CRP. In their study, BDE-47, BDE-99 and BDE-100 consistently showed a statistically significant positive correlation with CRP. CRP is an essential biomarker initiated in the inflammatory pathway and involved in endothelial tissue damage. The hepatic formation of CRP typically occurs through the elevation of inflammatory cytokines such as TNFa, IL-1, IL-8 and IL6 in the pathway leading to pre-eclampsia (Paternoster et al., 2006; Cemgil Arikan et al., 2012; Chen & Khalil, 2017). When cytokines increase, endothelial damage of the placenta is initiated by placental ischemia induced by incomplete trophoblastic invasion and uterine artery remodeling. Similarly, high levels of CRP have been associated with GDM in the first trimester and preterm birth in mid-pregnancy (Leipold et al., 2005). Early preterm labor is an undesired neonatal outcome also associated with inflammation and placental damage involved in pre-eclampsia (Paternoster et al., 2006)

5.2 Strength and Limitations

This review provides an overview of the state of knowledge thus far on PBDE levels in pregnancy and adverse maternal/infant health outcomes. It supports the possible mechanistic involvement of PBDE to adverse health effects in this vulnerable population. This review also consists of articles on studies conducted globally in different populations with a focus on different PBDE congeners and various health effects that add value in understanding the negative impacts of PBDE in pregnancy. The review identified potential factors that can affect the consistency of study findings and research gaps to support future work to advance primarily mechanistic understanding to support risk assessment of PBDE exposure in pregnancy.

Most studies in this review were assessed as moderate/high-quality (see Appendix Table 5). The observed consistencies in maternal outcomes with gestational diabetes may be due to similar and clear eligibility criteria. Studies of higher quality also had large sample sizes, an ethnically diverse cohort and adjusted for many confounders, as in Rahman et al.'s (2019) prospective study. Liu et al. (2018) matched cases and controls, which has the benefit of increasing efficiency by allowing for a similar distribution across the confounding variables (Rose and Laan, 2009). The systematic review provided a large set of potential a priori covariates and helped identify trends in specific congeners to look out for.

The limitations related to this literature review are as follows: about 15% of the studies were considered low quality based on the ONS rating. While 50% were considered as moderate quality, those studies still had limitations. The sample size, the rationale and transparency of reporting the study design, PBDE exposure analysis methodologies,

subject recruitment methods and self-reported information made some studies weaker compared to others (Oakes et al., 2017; Pourhoseingholi et al., 2013; Siddique et al., 2016; Zaccai et al., 2004; Lazarevic et al., 2022; Lin et al., 2011; Kim et al., 2009).

Most studies were cross-sectional and hence, their findings would need to be interpreted with caution. Few studies, even though they provide valuable insights on PBDE and adverse pregnancy-related effects, they do not allow for the generalization of study findings due to variability of the studies (Miranda et al. 2015; Chevrier et al., 2010; 2011; Smarr et al., 2016; Foster et al., 2011; Kim et al., 2009). Study heterogeneity can be attributed to various factors such as the study design, target populations, measurement tools for quantifying exposures and outcomes, the trimesters when the exposure or outcome was evaluated, ethnicity and/or socioeconomic status, congeners evaluated, biospecimens where exposure was measured, statistical methods, confounders used, etc.

High study heterogeneity associated with these articles also did not permit the conduct of a meta-analysis as differences in the study designs, methodology or statistical effect estimates, prevented a derivation of a meaningful summary of the effect estimate typically used for meta-analysis reports. As a result, a meta-analysis approach was not feasible and a systematic review using narrative synthesis was done. Narrative synthesis are sometimes common routes of approaches in public health when these issues occur. One of the limitations of this narrative approach for the systematic review is that they often lack replicability of the methodology approach. In this review, data was extracted a certain way, but other authors may want to collect data another way. Also, there are challenges in the transparency of the link of the findings (Campbell et al., 2019). Campbell et al. (2020)

proposed a small extension to the PRISMA called “Synthesis Without Meta-analysis (SWiM) items” that can increase transparency. One of the items that was reported and used for this review was “grouping studies for synthesis” In this review, articles were grouped by congener associations.

Additional limitations that were not mentioned include the lack of studies exploring racial, ethnic, and socioeconomic differences. Recent literature has emphasized the gap and the importance of considering ethnic differences when understanding health outcomes (Kanakamedala & Haga, 2012). One of the main issues with these epidemiological studies is that the cohorts were not always representative of the entire population, which can lead to bias and misleading results. Differences in exposure concentration and health outcome relationships among different ethnicities were not investigated because they were not discovered during the search. Buck Louis et al. (2018) conducted the only study in the United States that looked at racial and ethnic cohort differences (including non-Hispanic White, non-Hispanic Black, Hispanic, and Asian) and birth weight. All the cohorts demonstrated a non-significant, negative correlation between birth weight and BDE-28 or BDE-153 except for Hispanics that demonstrated a positive association with birth weight for BDE-153. Whether these findings are consistent must be verified with more studies identifying racial and ethnic differences especially in terms of social disparity differences, education level, and income. Varshavsky et al.’s (2020) study identified differences in PBDE among different ethnic and racial groups during mid-gestation in California. PBDE exposure ranged from high to low in the following order: Non-Hispanic Black > Latina/Hispanic > Non-Hispanic White > Asian/Pacific Islander/Other (p 0.01). Hence, there may be disparities among racial cohorts that are worth investigating. As mentioned by Karastergiou (2015) and Tian et al. (2016), this could be due to

body composition differences which identified differences in body fat content among different ethnicities.

Furthermore, the dose-response relationship was not examined by all the studies; however, it should be done in future reportings. Different methods such as tertiles or quartiles comparing high, median and low doses of PBDE exposure would allow for the comparability of the level of exposure to the effect of an outcome. Oulhote et al. (2018), for example, proposed a method for categorising PBDEs with values of LOD, LOD to the median above LOD, and >median categories. Most endocrine disrupting chemicals are non-monotonic in nature (Vandenberg et al., 2016). For instance, as mentioned in Chapter 4.4 in the Results section, Eick et al. (2020) identified a U-shape in their dose-response curve with the mid-tertile showing the most significant decrease in infant birth weight compared to the lowest and highest tertile with PBDE exposure. Hence, testing the contaminants as a continuous variable in the linear regression models may not provide a true depiction of the dose-response effect of the exposure of PBDE to the outcomes.

This systematic review study was not able to directly challenge biomarkers' role as an intermediate endpoint between the association of PBDE and health outcomes. The mechanism by which PBDE acts on the gestational tissues in humans during pregnancy are limited. Overall, how PBDEs functions during the different trimesters of pregnancy are also limited. In previous literature on prenatal stress, biomarkers as an intermediate have not shown a linear relationship with outcome measures. Part of this reason is that the human body is very complex, and biomarkers can target cell pathways leading directly or indirectly to adverse

health effects (Coussons-Read et al., 2013). While we see correlations on the surface, underlying mechanisms need to be seen to identify a definitive causal relationship and PBDEs' health risk in the community. Mechanistic studies need to be facilitated to understand how PBDEs may affect physiological changes in the body. With additional research, it may be possible to see the true nature of the relationship between the exposure and the outcome (Marchionni & Reijula, 2019).

There are challenges associated with looking at the mechanistic pathway using animal models. Animal models should be further looked at as preliminary studies; however, they should not be solely relied upon. There are challenges with translating the data findings from animal models to human species, including differences in the structure and physiology of the human body and animals. Animals are commonly used to identify dose-response relationships and toxicity mechanisms in environmental toxicity testing (Suvorov et al., 2021). However, it does not provide an accurate estimate of the risk in the human population.

Additionally, research should be conducted with accurate assessment tools specifically designed for measuring biomarkers during the critical trimesters of pregnancy and as a longitudinal study to compare changes along the pregnancy period. Standard guidelines also need to be established that outline the normal concentration ranges of biomarkers during pregnancy. In that manner, it would easier to identify whether the biomarkers that are measured are within or outside the normal ranges and whether it is a concern. For instance, the analytical tools to measure biomarkers such as thyroid hormones have weaknesses (Koulouri et al., 2013). Immunoassays are commonly used to measure thyroid concentrations in the body. However,

the interpretation of its level in the body may be inaccurate and may be affected by alterations in serum binding proteins. Thyroid can either interchange in the free form where it is unbound or bound to a thyroid-binding protein and provide false values in many physiological and disease states. Ultrafiltration LC-MS/MS is an alternative that has been recommended (Welsh & Soldin, 2016).

Future directions in this research should consider longitudinal prospective cohorts, study PBDE-related effects as mixtures and co-pollutant effects, also focus on gaining mechanistic information on PBDE toxicity and related mediation analysis for causal information in risk analysis. A more comprehensive exposure assessment with the prospective follow-up of vulnerable populations such as children is needed to understand the long-term phenomenon of PBDE's effect on health through high-content biomarker analysis.

5.3 Significance, Implications and Future Research

The synthesis of the articles provides compelling evidence that PBDEs are associated with adverse outcomes during pregnancy. Some of the common covariates identified between all the studies included maternal age, maternal education, smoking status, baby sex and more. The review also allowed us to see possible trends among specific congeners.

For researchers and policymakers, this study will benefit them in setting the initial stages for understanding the possible health implications of this chemical, whereas past literature reporting focused more on the biomonitoring aspect. One of the primary concerns with research involving pregnant women is that there is limited knowledge available for

initiating evidence-based informed prenatal care (Little & Wickremsinhe, 2017). This study can serve as a starting point for future work in this field in health research. Exploring human exposure is critical for filling in gaps related to toxicology. The review identifies gaps in knowledge about PBDEs that the researcher will need to look further into and methodological approaches that may need to be reassessed.

For policymakers, the review provides an understanding of the risk of PBDEs to maternity health consequences and necessary environmental regulations to prevent exposure to humans. In Canada specifically, there was one Canadian study conducted in 2016 that explored the perceptions of 23 pregnant women exposed to brominated flame retardant (BFR). Four themes had emerged including the lack of knowledge of PBDEs, factors influencing BFR exposure, responsibility to inform, and informed choice. While there are several steps that need to be taken to evaluate the health effects, public awareness is the primary step needed to make informed decisions (Lane et al., 2016).

According to the literature, other maternal and infant health complications have been shown to be associated with PBDE and are worth investigating further. These complications include maternal depression and changes in behavioral patterns such as self-reported hand-to-mouth behaviors, including biting nails and licking fingers (Peltier et al., 2022; Buttke et al., 2013). In addition to endocrine disruption, PBDEs are also considered to present neurotoxic and carcinogenic properties in experimental animal studies and human observational studies (Costa & Giordano, 2007; Costa et al., 2014; Siddiqi et al., 2003, Van De Bor, 2019). Exposure may cause long-term behavioural abnormalities specifically related to cognition and motor abilities (Linares et al., 2015). In school aged children, poorer attention and poorer mental

development, poorer psychomotor development and lower IQ at preschool-age children were observed in multiple studies (Berghuis et al., 2015; Eskenazi et al., 2013). There was also evidence of weak motor control of one's non-dominant hand and increased autistic behaviors in children (Eskenazi et al., 2013; Braun et al., 2014).

Currently, there are a few alternatives that have proposed to have been used to replace PBDEs as flame retardants, such as other brominated flame retardants and halogen-free flame retardants. The U.S. E'A's Design for the Environment program is investigating the risk of these alternatives. However, specific alternatives are unclear; hence, more information on these retardants is needed (Government of Canada, 2013). According to Taheran et al. (2017), nano clay or new polymers, such as bishydroxydeoxybenzoin are other possible alternatives. Conventional wastewater treatment plants have not been successful in degrading PBDE and, as a result, end up depositing in the soil. Advanced treatment processes, such as ultraviolet light, advanced oxidation, and photocatalytic degradation showed promising potential for removing 70–100% PBDEs from wastewater.

CHAPTER 6: CONCLUSION

There is suggestive evidence that exposure to various PBDE congeners measured in pregnant mothers can be harmful to mothers and their infants. Although studies on the relationship between PBDE and maternal/infant health outcomes, maternal biomarkers do not consistently show statistical significance in some studies but show suggestive trends; this does not necessarily mean an absence of an effect. Studies in the review are heterogeneous in nature and require more work for the validation of these observations. Future studies with large longitudinal prospective cohort designs, with reliable exposure monitoring, a rich set of covariate data collection, maternal biomarker analysis, and advanced statistical methods can add value to understanding the risk related to PBDE exposures in pregnancy. Furthermore, more toxicological studies are required to support the PBDE exposure-related adverse pregnancy outcome pathways analysis. It is through studies like this that it is possible to develop a better understanding of the effect of exposure to PBDE and human health risks and the incidence of adverse health effects in Canada and across the globe.

Declaration of Competing Interest

The authors declare no competing interests with this thesis and publication.

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APPENDIX

Table 1: Embase Search strategy (OVID EMBASE Classic + Embase 1947-;)

#	Searches
1	exp polybrominated diphenyl ether/
2	((polybrominated adj2 diphenyl ether*) or pbde*).ti,ab,kw.
3	1 or 2
4	(Gestational* or pregnan* or maternal*).ti,ab,kw.
5	(Infant* or newborn* or neonate*).ti,ab,kw.
6	maternal welfare/
7	newborn/
8	exp pregnancy/
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	limit 10 to yr=”2005 -Current”
12	limit 11 to English language
13	limit 12 to human
14	(conference abstract or conference review).pt.
15	13 not 14

Table 2: PubMed search strategy (https://pubmed.ncbi.nih.gov/)

#	**Searches**
1	Halogenated Diphenyl Ethers[Mesh]
2	polybrominated diphenyl ether*[Title/Abstract] OR pbde*[Title/Abstract]
3	#1 OR #2
4	Gestational*[Title/Abstract] OR pregnan*[Title/Abstract] OR maternal*[Title/Abstract]
5	(Infant*[Title/Abstract] OR newborn*[Title/Abstract] OR neonate*[Title/Abstract])
6	Maternal Health[Mesh]
7	Infant, Newborn[Mesh]
8	Pregnancy[Mesh]
9	#4 OR #5 OR #6 OR #7 OR #8
10	#3 AND #9
11	***add 2005-2022 limit
12	***add English limit
13	***add Humans

Table 3: Scopus search strategy (www.scopus.com)

1	TITLE-ABS-KEY (((polybrominated W/2 diphenyl AND ether*) OR pbde*))
2	TITLE-ABS-KEY ((gestational* OR pregnan* OR maternal*))
3	TITLE-ABS-KEY ((infant* OR newborn* OR neonate*))
4	#2 OR #3
5	#1 AND #4
6	***excluded up until 2005
7	*** add english limit
8	*** add human and humans limit

Table 4: Web of Science search strategy (www.webofscience.com via Clarivate)

1	TOPIC: (((polybrominated NEAR/2 diphenyl ether*) or pbde*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
2	TS=(Gestational* OR pregnan* OR maternal*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
3	TS=(Infant* OR newborn* OR neonate*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
4	#2 OR #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
5	#1 AND #4 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
6	#1 AND #4 Refined by: [excluding] PUBLICATION YEARS: (2004 OR 2003 OR 2002 OR 2001) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
7	#1 AND #4 Refined by: [excluding] PUBLICATION YEARS: (2004 OR 2003 OR 2002 OR 2001) AND LANGUAGES: (ENGLISH) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

Table 5: Summary of Newcastle Risk of Bias Assessment

		Selection				Comparability	Outcome				
First Author (year)	**Study design**	**Representativeness of the sample**	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome of interest not part at the start of the study?**	**Based on design and analysis**	**Assessment of outcome**	**Follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Score**	
Abdelouahab (2013)	Cohort		+	+	+	+	+	+	+	7/9	H
Buck Louis (2018)	Cohort	+	+	+	+	++	+	+	+	9/9	H
Harley (2011)	Cohort			+	+	+	+	+	+	6/9	M
Miranda (2015)	Cohort	+		+	+	+	+			5/9	M
Ouidir (2020)	Cohort	+	+	+	+	++	+	+	+	9/9	H
Rahman (2019)	Cohort	+	+	+	+	++	+	+	+	9/9	H
Robledo (2015)	Cohort			+	+	+		+		4/9	L
Serme-Gbedo (2016)	Cohort	+		+	+	++	+	+	+	8/9	H
Smarr (2016)	Cohort		+	+	+	++		+	+	7/9	H
Stapleton (2011)	Cohort	+		+	+	+	+			5/9	M
Vuong (2015)	Cohort	+	+	+		++	+	+	+	8/9	H
Vuong (2021)	Cohort	+		+	+	+	+	+	+	7/9	H
Wood (2017)	Cohort	+		+	+	++	+	+	+	8/9	H
Zota (2018)	Cohort	+	+	+	+	+	+	+		8/9	H
Zhang (2010)	Cohort	+	+		+		+	+		5/9	M
Zhuang (2021)	Cohort	+		+	+	+	+	+	+	7/9	H

		Selection				Comparability	Outcome				
		Representativeness of the sample	Nonrespondents	Ascertainment of exposure		The subjects in different outcome groups are comparable	Assessment of outcome	Statistical test			
Cabrera-Rodríguez (2019)	Cross-sectional	+		+		+	+	+		5/7	M
Chao (2007)	Cross-sectional	+		+		+	+	+		5/7	M
Chen (2015)	Cross-sectional	+	+	+		+	+	+		6/7	H
Chen (2018)	Cross-sectional	+	+	+		+	+	+		6/7	H
Chevrier (2010)	Cross-sectional			+		+	+	+		4/7	M
Chevrier (2011)	Cross-sectional	+		+		+	+	+		5/7	M
Ding (2017)	Cross-sectional		+	+		+	+	+		5/7	M
Eick (2020)	Cross-sectional	+		+		+	+	+		5/7	M
Foster (2011)	Cross-sectional	+		+		+	+	+		5/7	M
Gao (2016)	Cross-sectional	+		+		+	+	+		5/7	M
Herbstman (2008)	Cross-sectional	+		+		++	+	+		6/7	H
Hjermitslev (2020)	Cross-sectional	+		+		++	+	+		6/7	H
Kim (2009)	Cross-sectional			+			+	+		3/7	L
Kim (2013)	Cross-sectional			+		+	+	+		4/7	M
Kim (2015)	Cross-sectional			+		+	+	+		4/7	M
Lazarevis (2022)	Cross-sectional	+				++		+		4/7	M
Lignell (2013)	Cross-sectional	+		+		++	+	+		6/7	H
Lignell (2016)	Cross-sectional	+		+		++	+	+		6/7	H
Lin (2011)	Cross-sectional			+		+	+	+		4/7	M
LopezEspinosa	Cross-sectional	+	+	+		+	+	+		6/7	H

(2013)											
Lv (2015)	Cross-sectional	+	+	+		+	+	+		6/7	H
Matovu (2019)_	Crosssectional			+		+		+		3/7	L
Mehta (2021)	Crosssectional	+		+		+	+	+		5/7	M
Müller (2016)	Crosssectional	+		+		+	+	+		5/7	M
Stasinka (2014)	Crosssectional	+		+		+		+		4/7	M
Tan (2009)	Crosssectional	+		+				+		3/7	L
Xu (2013)	Crosssectional	+						+		2/7	L
Yin (2019)	Crosssectional			+			+	+		3/7	M
Wu (2010)	Crosssectional	+						+		2/7	L
Zota (2011)	Crosssectional			+		+	+	+		4/7	M
		Selection				**Comparability**	**Exposure**				
		Case definition adequate?	**Representati ve of cases**	**Selection of control**	**Definition of control**	**Based on design and analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls?**	**Non-response rate**		
Eslami (2016a)	Case-control	+			+	+	+	+		5/9	M
Eslami (2016b)	Case-control	+			+	+	+	+		5/9	M
Jin (2020a)	Case-control	+			+	+		+		4/9	M
Jin (2020b)	Case-control	+	+			+	+	+		5/9	M
Liu (2018)	Case-control	+			+	+	+	+		5/9	M
Peltier (2015)	Case-control	+				+	+			3/9	L
Peltier (2021)	Case-control	+	+	+	+	+	+			6/9	M
Zhao (2019)	Case-control	+	+		+	+	+	+		6/9	M

***Comparability for cohort study designs have a maximum score of 2 stars for adjustment of confounders and additional adjustment of confounders**

Table 6: Summary table of studies on maternal health effects (N=7)

Authors (year)	Country	Study design & sample size	Population characteristic	Exposure	Trimester (outcome measurement)	covariates	Findings (Beta coefficient /OR/RR)	NOS Quality
Gestational Diabetes Mellitus (GDM)/ Glycemic index (GI) (n=6)								
Eslami et al. (2016b)	Iran	Case-control; N=70 GDM cases & N=470 with normal pregnancy	Primiparous, singleton, avg MA of cases: 28.76+/-4.8 years & controls: 26.66+/-4.69 years. 50% of cases & controls had only HS degree	Maternal serum ΣPBDE (BDE-28, 99, 153), ΣPOP (PBDE and PCB) in 3rd trimester	3rd	*OR model:* MA, prepregnancy BMI,, GA, & total lipids in maternal serum. I*ndividual congener model:* MA, ppBMI, GA & total lipid	**GDM**: ↑ ΣPBDE sig ↑GDM by 121% (OR=2.21, 95%CI: 1.48–3.30) ↑ΣPOPs sig ↑ GDM by 61%(OR=1.61, 95%CI:1.19–1.65) In individual PBDE model, PBDE 99 & 28 sig ↑GDM (OR=2.14, 95%CI: 1.993.83, p=0.004; OR=2.73, 95%CI: 1.22-6.11, p=0.003). BDE-153 marginally sig ↑GDM (OR= 1.81 (1–3.26))p=0.05	M
Liu et al (2018)	China	Matched Casecontrol; N= 77 GDM cases and N=154 controls	avg MA case: 28.9 ± 4.6 years vs control: 28.9 ± 2.8 years. Overweight/ obesity (BMI > 24 kg/m^2) was > in GDM (26%) vs. 15.6% in non-GDM, but no sig difference in BMI b/w the two groups (22.4 ± 3.0 vs. 21.7 ± 2.8 kg/m^2). OGT results for control group, the fasting blood glucose was 4.8 ± 0.7, 1hr postprandial glucose was 10.0 ± 2.0 & 2hr and 8.4 ± 1.4.	Maternal serum BDE-28, 47, -99, -100, -153, -154, -183 & Σ7PBDE in 1st trimester	24–28 weeks of gestation	single and multiple PBDE model: pregnancy BMI, serum triglycerides and total cholesterol	**GDM**: single-BDES: BDE-153 (OR= 4.04, 95%CI: 1.92, 8.52), BDE-154 (OR= 1.88, 95%CI: 1.15, 3.09) & BDE-183 (OR=1.91, 95%CI: 1.31, 2.08) sig ↑ GDM. Multiple- BDEs: Ors sig ↑ for BDE-153 (OR = 2.76, 95% CI: 1.07, 7.11) & BDE183 (OR= 1.56, 95% CI: 1.02, 2.40), not for BDE-154. BDE-154 had strongest association w/h GDM in 3rd Q (OR = 2.58; 95% CI: 1.16, 5.72) & ↓OR in 4th Q (OR = 1.70; 95% CI: 0.73, 3.99) vs. lowest Q	M
Rahman et al. (2019)	USA	Prospective longitudinal cohort; N= 2334	Avg MA cases: 28.2±5.5 years, lowrisk women w/h ppBMI within normal/overweight range (BMI 19.0– 29.9 kg/m^2)	Maternal serum BDE-28, 47, -99, -100, -153, -154, 183 at 8–13 weeks of gestation	16–22, 24–29, 30–33, 34–37, and 38–41 wks of gestation	MA, ppBMI, LEA, parity, race/ ethnicity, family history of T2D among first-degree relatives, serum cotinine, and serum total lipids	**GDM**: Sig ↑ GDM w/h women w/o family history of type 2 diabetes for BDE-47 (RR=1.18; 95% CI: 1.08–1.29 per 1-SD ↑) and BDE-154 (RR=1.23; 95% CI:1.12–1.34 per 1-SD ↑)	H
Smarr et al. (2016)	USA	Prospective longitudinal cohort; N= 258 GDM cases: 28 and N=230 controls	avg MA and BMI is 29.7 ± 3.7 years and 26.2 kg/m^2, mostly parous, non-Hispanic White women, non-smokers, prevalence of prospectively observed GDM and GHTN was 11% (n = 28) and 10% (n = 27),	Maternal serum BDE-28, 47, -99, -100, -153, -154,183 in first trimester	≥24 wks gestation	serum lipids, MA, BMI, non-white race, smoking, & sum of remaining chemicals in the relevant class of compounds	**GDM:** 1 SD (0.20 ng/mL) ↑ in BDE-153 sig ↑GDM by 37–79% in adj models of sum of remaining PBDEs (OR = 1.79; 95%CI: 1.18, 2.74). BDE-100 had a 2.22x ↑ odds of GDM per 1 SD (0.09 ng/mL)(OR = 2.22, 95% CI: 0.96, 5.17) BDE-47 ↓ GDM (OR = 0.32; 95%CI: 0.10, 1.01)	M
Mehta et al. (2021)	USA	Cross-sectional; N=95	racially/ethnically diverse (45.3%), INC ≤ 100% of Federal poverty level, & 49.5% obese BMI, half nulliparous, overweight, GM concentrations of fasting glucose was 4.42 ± 0.04 mmol/L, fasting insulin was 81.19 ± 4.73 pmol/L, and HOMA-IR was 1.65 ± 0.09 units.	Maternal serum BDE-47, -99, −100, − 153, 5-OHBDE-47, 6-OHBDE-47 in late 1st or 2nd trimester	1st/2nd (baseline, 10–24 wks gestation)	MA, race/ethnicity, GA at baseline, household income, ppBMI and parity	**GI**: Doubling of BDE-153 & 5-OHBDE-47 had a 151% (β= -1.51, 95%CI: -2.84, 0.16, p=0.03) and marginally sig 57% (β =-0.57, 95%CI: -1.21, 0.06, p=0.08) ↓ in fasting plasma glucose. Mostly consistent inverse association w/h most PBDEs/OH-PBDEs and fasting glucose but ∑PBDEs & 6- OHBDE-47, nonsig positive associations.	M
Vuong et al. (2021)	USA	Prospective longitudinal cohort; N=388	majority of women were non-Hispanic White (61.8%), b/w ages of 25–34 years (59.4%), and had some college education or higher (73.8%). Most women were either married or living with a partner (79.3%), had a serum cotinine level < 1 ng/mL (82.7%), and had a BMI ≥ 25 kg/m^2 (57.4%). BDE-47 (20.7 ± 2.6 ng/g lipid)	Maternal serum single pollutant BDE (BDE-28, 47, -99, -100, -153) and multipollutant (ΣPBDE) at 16 weeks	Maternal serum glucose at >24 wks gestation	age, race/ethnicity, household income, SS, marijuana use, serum ∑PCBs, ppBMI, and parity.	**GI:** a 10-fold ↑ in BDE-28 associated with a 13.1 mg/dL (95% CI: 2.9, 23.2) ↑ in glucose.	H
Gestational Hypertension/preeclampsia (n=2)								
Smarr et al. (2016)	USA	Case-control; N=27 GHTN cases and N=231 GHTN controls	avg MA and BMI was 29.7 ± 3.7 years and 26.2 kg/m^2, mostly parous, non-Hispanic White women, nonsmokers, prevalence of prospectively observed GHTN was 10% (n = 27),	Maternal serum BDE-28, 47, -85, -99, -100, -153,154 in first trimester	≥24 wks gestation	MA, ppBMI, GA and total lipids in maternal serum	**GHTN**: 1 SD ↑ in BDE-66 had a non-sig 56% ↑ odds in GHTN (OR =1.56; 95%CI: 0.93, 2.64). BDE-47 had an 86% ↑ odds of GHTN (OR=1.86, 95% CI(0.55,6.27).	M
Eslami et al. (2016a)	Iran	Prospective longitudinal cohort; N= 45 preeclampsia cases & N=70 control	avg MA was 27.3 ± 5.39 years; avg BMI for cases and controls was 26.2 ± 4.86 vs 22.9 ± 4.17 kg/m^2, 50% with min HS diploma; non- smokers or alcohol usage; iron & folic acid supplementation during their pregnancy	Maternal serum ΣPBDE (PBDE28, 47, 99, 100, 153, 154, 183, and 209) in 3rd trimester	≥24 wks gestation	*All models:* GA, ppBMI, MWG, total lipids in maternal serum	**Pre-eclampsia:** Sig association b/w total PBDEs and pre-eclampsia (OR=2.19, 95%CI: 1.39– 3.45)	M

Abbreviations: PSE:post secondary education; LEA: low education attainment; HS: high school; ft4: free thyroxine; TT4: total thyroxine; TSH: thyroid stimulating hormone; UCB: umbilical cord blood; GA: gestational age; MA: Maternal age at enrollment; MWG: maternal weight gain; SS: smoking status; DEL: delivery; INC: Household income

Table 7: Summary table of studies on PBDE and infant health effects (N=29)

Authors	Country	Study design & sample size	Population characteristic	Exposure	Outcome	covariates	Findings (Beta coefficient /OR/RR)	NOS Quality
Birth size (n=22) **Birth weight/ birth length LGA/SGA /head circumference**								
Buck Louis et al. (2018)	USA	Prospective longitudinal cohort; N=2106	93% non-Hispanic White, 91% non-Hispanic Black, 92% Hispanic, & 90% Asian, avg age of 30, 25, 27, & 31 years, ppBMIs of 23.2, 24.1, 24.3, and 22.2,. Married college educated with health insurance and a comparable % of (null)parous women.	Maternal plasma BDE-28 and 153 in 1st trimester	BW, BL, HC at delivery	BL model: MA, education, ppBMI, serum lipids, serum cotinine, infant sex, & a chemical-maternal race/ethnic interaction term. Delivery mode was added in HC models.	**BW**: BDE-28 & BDE-153 non-sig ↓ BW among the whole cohort, White, Black, Hispanic and Asians. **BL**: BDE-28 ↓ BL (β = −0.22, 95% CI: − 0.39, −0.05, p<0.05) only among Hispanic women & BDE-153 (β = −0.37, 95% CI: −0.56, −0.18, p<0.01) only among Black women. **HC**: No significant association	H
Cabrera-Rodríguez et al (2019)	Spain	Cross-sectional; N=447	Avg MA 31 years, multiparous (62.0%), no previous miscarriages (72.3%), free of pregnancy diseases — GDM, HTN, or hypothyroidism— (72.0%) and non-smoker (88.8%) avg BW: 3284g, girls (52.6%) w/h Apgar score ≥ 9 (90.8%) & no malformation. PTB newborns had SGA (16/18 births, 88.8%) at > proportion than non-PTB (29/429 births, 6.7%).	UCB BDE-47 at delivery	BW, SGA, Apgar score at delivery	GA, maternal smoking, nulliparity, number of OCPs	**BW**: No significant association in the whole cohort ***Sex stratified:*** *Males:* No sig associations *Females*: BDE-47 sig ↓ BW only (Spearman r = - 0.643, p = 0.001). When BW was dichotomized, ↑ odds of SGA **Apgar score:** 9.2% of the total cohort, 17.8% of the SGA, and 8.4% of the LGA reported an Apgar score between 7-8. Females had an Apgar score ≥ 9 (90.8% of females)	H
Chao et al (2007)	China	Cross-sectional; N=20	Avg MA 29.0 ± 3.44 years, ppBMI was 22.0± 3.95 kg/m^2, >90% non-alcoholic or non-smokers, 40% male infants, GA of 38.7 ± 1.73 wks, BW of 3.13 ± 0.388 kg, BL of 50.8 ± 2.37 cm, & HC of 33.1 ± 1.46 cm.	Breast milk BDE- 47, 85, 99, 100, 153, 209 at delivery	BW, HC at delivery	All model: MA, maternal ppBMI, and parity	**BW**: overall↓ BW. BDE had higher GM BW in the LBW group (≦ 3.05kg in sample (n=7)) as compared to the higher BW group (>3.05kg in sample n=13). BDE47 : GM= 2.15 (95% CI :1.57–2.95) vs. 1.05 (95% CI :0.837–1.32), both p=0.001 BDE99 : GM=0.727 (0.419–1.26) vs. 0.296 (95% CI :0.211–0.422), both p=0.001 BDE100 : GM=0.451 (95% CI :0.347–0.586) vs. 0.318 (95% CI :0.283–0.357), both p=0.007 **HC**: Non-sig lower HC with higher BDE exposure	M
Chen et al (2015)	China	Cross-sectional; N=215	Avg MA and ppBMI 28.03 ± 4.88 years & 21.61 ± 2.88 kg/m^2; majority (64.7%) primiparous; 51.60% with <9yrs of education; majority with <3000 (483.6 US$); avg BW, BL and HC was 3415.42 ± 455.05g, 51.10 ± 3.00cm, and 33.59 ± 1.67cm	Maternal serum PBDE-28, -47, -99, -100, -153, Σ5PBDE at delivery	BW, BL, HC at delivery	MA, parity, education, ppBMI, MWG, family income, infant sex, and GA	**BW**: BDE-28 had marginal sig ↓ BW (β = -126.31, 95% CI: -253.69, 1.08); All other PBDE except BDE-153 non-sig ↓ with BW. ***Sex stratified:*** *Males:* BDE-28 sig ↓ BW (β = -253.76, 95% CI: -438.16, 69.36). BDE-47, -99, 153 are non-sig ↓ to BW. *Females:* BDE-153 and ↑ BW (β = 212.36, 95% CI: 31.41, 393.31). All other BDEs non-sig ↓ BW. **BL**: BDE-28 & BDE-100 sig ↓ BL (β = 0.920, 95% CI:1.82, 0.02; β = 0.972, 95% CI:1.83, 0.08). BDE-99 and BDE-153 non-sig ↓ with BL. ***Sex stratified:*** *Males*: BDE-28 marginally-sig ↓ BL (β = -1.03, 95% CI: -2.12, -0.07), BDE-100 had non-sig ↓ among males (β = -0.69, 95% CI: -1.88, -0.50), BDE-99 sig↓ BL (β = -1.50, 95% CI: -2.84, -0.16). *Females:* BDE-28 marginally-sig ↓ BL (β = -1.12, 95% CI: -2.77, -0.53); BDE-100 had sig ↓ with BL (β = -1.47, 95% CI: -2.92, -0.03) **HC**: Non sig association, non-sig ↓ HC with BDE-28 in whole, male and female cohort	M

Chen et al (2018)	China	Cross-sectional; N=222	Avg MA and ppBMI was 28.21 ± 4.89 years & 21.49 ± 2.95 kg/m^2; mostly nulliparious (65.80%); 50.90% do not have HS degree; family income <RMB 3000 ¥ (67.60%); no smokers/alcohol drinkers; mean HC was 33.43 ± 1.77cm	UCB BDE-28, BDE-47, BDE-99, BDE-100, Σ4PBDE at delivery	BW, BL, HC at delivery	MA, parity, education, ppBMI, MWG, family income, infant sex, and GA	**BW**: In total cohort, female only cohort & male only cohort, all PBDEs had non-sig ↓ BW. ***Sex stratified:*** *Males*: All BDEs had non-sig, ↓ BW *Females*: only BDE-28, BDE-99 and Σ5PBDE had non-sig, ↓ BW. **BL**: In total cohort, female only cohort & male only cohort, all PBDEs non-sig ↑ BL. **HC**: Cord serum BDE-47 associated with ↑ HC (β =0.42, 95% CI 0.00, 0.84). ***Sex stratified:*** *Males*: BDE-28 had non-sig ↓HC *Females*: BDE-47 (β = 0.78, 95% CI 0.21, 1.35) and ∑4PBDEs (β = 0.90, 95% CI 0.11, 1.69) sig ↑ HC	M
Eick et al (2020)	USA	Cross-sectional; N=506	Avg MA: 32±5.4 years, self-identified as Non-Hispanic (NH) White (38.6%) or Hispanic (34%), around 1/2 had normal ppBMI (47.6%) and ≥1 prior births (50%). Most w/h college degree (22.9%) or graduate education (37.5%).	Maternal serum BDE 47, 99, ΣPBDE between 1st & 3rd trimester	BW in 2nd trimester	MA, parity, education, ppBMI, MWG, family income, infant sex, & GA	**BW:** In total cohort, middle tertile (8.47-14.22ng/ml) of BDE-47, BDE-99, & total PBDE sig ↓ BW z-scores of – 0.26 (95%CI = -0.48, −0.04)(n=172), −0.25 (95%CI = -0.47, −0.04) (n=170), & −0.26 (95%CI = -0.48, − 0.04) (n=170). ***Sex stratified:*** BDE-47 had stronger ↓ in BW z-scores in females (β =-0.08, 95%CI = -0.67, 0.52) in middle tertile vs. males (β=-0.04, 95% CI: -0.68, 0.60)	M
Foster et al. (2011)	Canada	Prospective longitudinal cohort; N=97	Avg MA was 33.1 ± 0.5 years. Mainly Caucasian (87%), Middle Eastern (e.g. Iran, Iraq, & Saudi Arabia; 6%) or Hispanic (4%). 84.5% reported having a university degree or > & 19.2% reported household incomes <$50 000, 48.9% b/w $50 000 & 100 000yrs, & 31.9% >$100 000/yr, 7.2% smokers, 43.3% reported at least one previous pregnancy loss w/h a mean of 1.9 ± 0.2 pregnancy losses. Around 35% had a pregnancy complication of some nature (e.g. GDM, GHTN, placenta previa, placenta abruption, PPROM and steroid exposure 8.3%	Maternal serum at 2nd trimester and delivery and UCB at delivery of BDE-17 (n=89), -28, 47, -66, -99 (n=97) , 100, -153, -154, -183, ΣPBDE	BW in 2nd trimester	BMI, MA, parity, GA at birth, socio-economic status (family income and years of education), sex of the baby, and serum cotinine concentration	**BW**: Only UCB BDE-99 (β=-3.951 p=0.016) and BDE-17 (β=- 49.86, p = 0.032) sig ↓ BW after confounder adjustment	M
Harley et al (2011)	USA	Prospective longitudinal cohort; N=286	low-income, primarily farm-worker community. Mothers were almost exclusively Latina, with 84% having been born in Mexico and half having lived in the United States for less than 5 years. Mothers tended to be young (median age =25 years),	Maternal serum BDE-28, -47, -85, -99,-100,-153, 154, 183 in 2nd trimester	BW, BL, HC at delivery	MA, marital status, parity, BMI, country of birth (United States vs. other), family income, and sex of infant plus net weight gain. HC model (model 1): MA, marital status, parity, BMI, country of birth (United States vs. other), family income, and sex of infant. Model 2: additionally adjusted for net weight gain	**BW**: 10-fold ↑ BDE-47 (β = -115g 95% CI: -229, -2), BDE-99 (β= -114 g, 95% CI: -225, -4) and BDE-100 (β =-121 g, 95% CI: -235, -7) sig ↓ in BW. **BL & HC**: All PBDEs had non-sig ↓ BL and HC	H

Hjermitslev et al (2020)	Greenland	Cross-sectional; N=482	Avg MA of 27. 5 ± 4.96 years, normal ppBMI (24.4 kg/m^2), and many were smokers (32%). Median BW was 3615 g, median BL 51 cm, median HC 35 cm and median GA at birth week 39	1st trimester Maternal serum ∑PBDE (47, 99, 100)	BW, BL, HC at delivery	All models: MA, plasma cotinine, parity, alcohol consumption during pregnancy and ppBMI	**BW**: ∑PBDE non-sig ↓ w/h BW (β=-51.4, 95%CI: -175, 72.0) but sig ↑ LBW (adjOR = 3.60, p = 0.017, data not shown). **BL** : ∑PBDE non-sig↓ w/h BL (β= -0.30, 95%CI : -0.89, 0.29)). **HC** : : ∑PBDE non-sig ↓ w/h HC (β= -0.13, 95CI% : -0.51, 0.25))	M
Lazarevic et al. (2022)	Australia	Cross-sectional; N=166	avg MA was 32 yrs old and avg BMI was 24.4 kg/m^2, predominantly educated at a tertiary or higher level (70%), resided in an urban location (70%), resided > 1 km from industry (77%), and had a gross household income > the national median of AU$80,000 (70%). Primarily full-term neonates and mothers who were not taking vitamins (72%), iron or folic acid (78%) during pregnancy	PBDE mixture (BDE-47 & BDE-153) in multipollutant model containing organochlorine pesticides, and metal in 3rd trimester	BW at delivery	PBDE, organochlorine pesticides, metals, pp-BMI, GWG, MA, primiparity, iron and folic acid supplementation, pregnancy vitamin use, level of education, household income, residential remoteness, distance to industry, fish consumption, sex of the neonate, and maternal height. ^ Urinary exposure concentrations were creatinine-ratio corrected and additionally adjusted for	**BW**: PBDE mixture (BDE-47 and BDE-153) was not sig associated with BW	M
Lignell et al (2013)	Sweden	Cross-sectional; N=364	Avg MA and ppBMI was 28.8 years and 23.4 kg/m^2; MWG was 23kg; 55% had <1-3 yrs of higher level of education or less (e.g. HS); mostly non-smokers; avg BW was 3589g	3rd week after delivery Breast milk ∑PBDE (BDE-47, -99, -100, -153)	BW at delivery	MA, ppBMI, MWG, education, SS and infant sex	**BW**: overall ↓ BW. ∑PBDE: −54 to −117 (p=0.05) and became sig GL added as confounder, did not change result (β = −106, p=0.004, n= 254). Excluding di-ortho PCB as confounder made association non-sig, β changed from −106 to −47 (n=not reported) Association with ∑PBDE and BW was stronger when fish consumption was included in the model, β ↓ by 29% from −106 to −137 (p = 0.01; n=not reported). ***Sex stratified:*** *Males:* ∑PBDE sig ↓ BW (β=−162, p=0.03, n=144) *Females:* ∑PBDE non-sig ↓ BW (β= −20, p=0.80, N=110) When GL added as a covariate, males still stronger association than females (β=-139 p=0.03 n=144 vs. β= - 47 n=0.6 n=110). Excluding missing data, GL did not change results however, in male infants was stronger (β changed from −126 to −162).	M
Lopez-Espinosa et al. (2015)	Spain	Prospective longitudinal cohort; N=670	Avg MA was 31 ± 4.6 years. Most women (94%) were born in Spain, 47%(325/686) women were manual workers (labelled as social class 3). Must primiparous (60%), 56% were passive smokers and 10% were alcoholics. The mean BMI was 26.4 ± 3.5 kg/m^2; mean HC was 34.1±1.6cm	1st, 3rd & delivery Maternal serum and UCB BDE-47, 99, 153, 154, 209 and ΣPBDE; UCB ΣPBDEs	BW, BL, HC at delivery	Different regression models varied in the covariates used. BW: smoking at week 12, season of last menstrual period BL: smoking at week 12 HC: smoking at week 12, education. Except for BDE-47 model which additionally included season of la. Sensitivity models: maternal PBDE analyses were adjusted for maternal levels of either ∑PCBs or HCB and maternal lipids, and cord PBDE analyses for these two contaminants and lipids measured in cord serum.	**BW**: maternal BDE-99 ↓ BW (−1.4%, 95%CI: −2.7, −0.2, p<0.05), resulting in a mean difference of around 46.8 g. When MWG or TSH levels were added, PBDEs and BW association was slightly reduced and became null (data not shown). For maternal BDE-47, addition of TSH in the model had a smaller impact on the association than addition of MWG. **HC**: maternal BDE-99 and ΣPBDE ↓ HC (-2.1%, 95% CI: −3.4, −0.8) p<0.01; β = −2.9%, 95% CI: −5.5, −0.3, p<0.05] by 0.7cm and 1.0cm. Maternal BDE-47 marginally ↓ HC by 0.34 cm (−1.0%, 95%CI: −2.2, 0.1) **BL**: Cord BDE-47 ↑ BL in female (2.0%, 95% CI: −1.1, 5.0) and ↓ in males (−1.4%, 95% CI: −4.4, 1.6], p-interaction = 0.04).	M

						Finally, we investigated differences by sex including the interaction of this variable with the contaminants in the main analysis.		
Matovu et al. (2019)	Africa	Cross-sectional; N=50	Avg MA and ppBMI were 29.4 ± 4.78 years and 29.8 ± 6.02 kg/m2 44% of the donor mothers were overweight (BMI, 25–<30 kg/m^2) whereas 40% of them were obese (BMI 30 kg/m2 or higher).	Breast milk PBDE at delivery	BW at 2-8 days after delivery	None for the spearman rho model	**BW**: Non sig ↑ BW with logBDE-47, logBDE-77, logBDE-99, logBDE-153 and log∑4BDEs. Non sig ↓ with logBDE-47 and BW (ρ= −0.149, p=0.458)	L
Miranda et al. (2015)	USA	Cross-sectional; N=136	Avg MA of 23 ± 4 years. Predominantly low-income, non-Hispanic black women.	Maternal serum BDE138/158, 153, 170, 180 in 3rd trimester	BW, BL, HC at delivery	MA, non-Hispanic black race, and maternal educational attainment level, parity, infant sex, and maternal smoking during pregnancy. Additional model had a PBDE/OH-BDE by thyroid hormone interaction term. In a sensitivity analysis further adjusted for ppBMI;	**BW:** Marginal ↓ BW w/h BDE 153. Adj for thyroid hormones did not alter findings (data not shown). **BL:** No sig association **HC:** Non-sig association with all PBDEs and ↓ HC In unadj model, BDE-153 (β = −0.32, 95% CI: −0.53, −0.12) and Σ PBDE (β = −0.23, 95% CI: −0.44, −0.02) sig ↓ HC by 0.32cm and 0.23cm, In adj model, BDE 47, 99, 153, and ΣPBDE ↓ HC ranging from −0.08 (e.g., BDE 47, 95% CI: −0.26, 0.11) to −0.20 (BDE 153, 95% CI:−0.42, 0.02)	M
Müller et al. (2016)	Africa	Cross-sectional; N=95	Avg MA and ppBMI were 22.5 years and 22.9 kg/m^2, majority within the normal BMI (18.5–24.9kg/m^2), two were underweight (<18.5 kg/m^2), fifteen were overweight (25.0–29.9 kg/m^2) and two were obese (above 30.0 kg/m^2). Occupation was separated by 41% of farming occupation and non- farming occupations w/h income either below 50 000 TZS (below 27 USD) and 51 000–500 000 TZS (27.5–270 USD) per month, 51% of rural residence, 60% of basic education (primary/ secondary school).	Breast milk BDE-47, -99, -100, -153, ∑PBDE at delivery	BW, BL at delivery	None mentioned	**BW:** BDE47, 99, 100, 153, ∑PBDE ↑ BW. ***Sex stratified:*** Only in females significant ↑ BW not in males: logBDE-47: (β= 0.43, p = 0.003), logBDE-99 (β= 0.4, p = 0.005), logBDE-100 (β= 0.43, p = 0.003), logBDE153 (β= 0.38 (p = 0.011) and for ΣBDE (β= 0.42, p = 0.005).	M
Ouidir et al. (2020)	USA	Prospective longitudinal cohort; N=2284	Avg age and ppBMI were 28.2 ± 5.5 years, and 23.6 ± 3.0 kg/m^2	Maternal plasma BDE154 from gestational weeks 16 to 40	HC in 2nd trimester	HC model: maternal race/ethnicity, MA, ppBMI, parity, highest level of education, marital status, infant sex, GA at the time of ultrasound, total plasma lipids (except for PFASs) and log transformed plasma cotinine level. Further assessed potential effect modification by infant sex*maternal race/ ethnicity.	**HC:** Sig ↓ with BDE-154 & HC in whole cohort (β = -0.34mm, 95%CI,−0.51 to−0.17mm) ***Sex stratified:*** *Males*: BDE154 sig ↓ HC (β = -0.34mm, p=0.001-0.01) *Females*: BDE154 sig ↓ HC (β = -0.33, p<0.01-0.05)	H

Robledo et al. (2015)	USA	Prospective longitudinal cohort; N=501	Avg MA 29.8 ± 3.7 years, 84% Non-Hispanic white, 96% with college degree, 95% passive smokers at baseline, 78% alcohol users at baseline but at 9-12wks 99.6% non-alcoholic users, BMI was 26.4 ± 6.5, almost primiparous (0.7 ± 0.8), had pre-existing diseases of GDM (n = 27), hypercholesterolemia (n = 18), and HTN (n = 7).	Maternal PBDE-28, -66, -85, -99 and -183 in 1st trimester	BW, BL, HC at delivery	maternal and paternal serum lipids, serum cotinine, maternal ppBMI (kg/m2), MA, difference in parental age, infant sex, and the individual and partner sum of remaining chemical concentrations in each chemical's respective class.	**BW**: Different results in avg BW changes in boys and girls. ***Sex stratified:*** *Males*: every 1-SD ↑ in lnPBDEs 66 and 99, avg BW only among boys ↑ by 125.04 g (95% CI: 18.16, 231.92) and 133.39 g (95% CI: 9.12, 257.37) *Females*: BDE-28 (β = –151.33 g; 95% CI: –298.56, –4.10) and BDE-183 (β =–84.60g; 95% CI –154.39, –14.82) ↓ BW **BL:** ***Sex stratified:*** BDE-28 sig ↓ BL in males (β = –0.18, 95% CI: –0.76, -0.41) and female (β = – 1.14, 95% CI: –2.00, –0.28) **HC**: ***Sex stratified:*** *Males*: BDE-28 sig ↓ HC (β = –0.24, 95% CI: –0.67, 0.19) while BDE-66, BDE-85, BDE-99 ↑HC (β = 0.60, 95% CI: 0.02, 1.18; β = 1.04, 95% CI: 0.04, 2.03; β = 0.91, 95% CI: 0.23, 1.60) *Females*: BDE-28 (β =–1.05, 95% CI: –1.73, –0.38) and BDE-66 (β = –0.17, 95% CI: –0.76, 0.41) sig ↓ HC; while BDE-85 (β =0.34, 95% CI: –0.78, 1.45) sig ↑ HC	M
Serme-Gbedo et al. (2016)	Canada	Prospective longitudinal cohort; N=349	Avg age at birth and BMI at recruitment were 28.8+/-4.4 and 16 to 49 Kg/m2, majority married or in a common-law relationship (93 %) and multiparous (68%). Among multiparous women 12 % and 7 % had history of LBW or pre- mature delivery, some had infections during pregnancy (9%), Previous preterm infant in multipara (n = 236) (7%) few smoked (19%) avg BW 3,366.6+/504.1, sixteen babies (4.6%) w/h LBW and 23 (6.6%) born prematurely (G < 37 wks).	Maternal plasma BDE47, BDE-99, BDE-100, BDE-153 & ΣPBDEs in 1st trimester	BW at delivery	MA at delivery, marital status, BMI at recruitment, infection, SS during pregnancy, ΣPCBs (CB-138, CB153 and CB-180), mother's total blood levels of lead (ng/ml) and previous pregnancies history in multipara only,	**BW**: non-sig ↓ in BW with all BDEs ΣPBDEs (β = -44.7, 95% CI : −173.6; 84.1), BDE47 (β =-14.4, 95% CI : -129.9, 101.2), BDE99 (β = -1.6, 95% CI : -90.9, 87.7), BDE100 (β = 4.7, 95% CI : 67.2, 76.5), and BDE153 (β = -55.9, 95% CI : -118.9, 6.9)	H
Stasinska et al. (2014)	Australia	Cross-sectional; N=173	Avg age was 32.1 ± 4.1 years, 56.4% were in the middle of their 1st pregnancy, 69.6% of women having income >80,000, & 46.6% living in their home for 10-50years	Maternal plasma BDE47, BDE-99, BDE-100, BDE-153 BDE-154 and Σ5 PBDEs at delivery	BW at delivery	MA, parity, GA, infant gender, maternal BMI before pregnancy, MWG during pregnancy, concentrations of PBDEs	**BW:** BDE-47, BDE-100, BDE-153 and ΣPBDEs non-sig ↓ BW; BDE-99 ↑ BW	M
Yin et al (2019)	China	Cross-sectional; N=60	Avg age 29.0 ± 4.7 years, ppBMI 20.7 ± 2.9 kg/m^2; mean HC was 33.9 ± 1.3cm	Colostrum BDE-28, BDE-47, BDE-99, BDE-100, BDE153 and BDE-154 at delivery	BW, HC at delivery	Basic adjusted model: neonate's gender, MA, ppBMI, and gestational period. Further adjusted model: adjusted further for GWG, parity, number of aborted pregnancies, drinking water source, alcohol drinking, occupation, and the diet preference.	**BW**: BDE-28 ↑ BW (β = 0.428, 95% CI: 0.000, 0.002, p=0.011) in further adjusted model; BDE-154 sig ↓ BW (β = −0.636, 95% CI: −0.003, 0.000, p=0.028) in basic adjusted model	M

Woods et al. (2017)	USA	Prospective longitudinal cohort; N=272	around 62% were white decent and rest was black/other	Maternal serum PBDEs (17, 28, 47, 66, 85, 99, 100, 153, 183) in 2nd trimester	BW at delivery	maternal race, MA at delivery, infant sex, maternal education, tobacco exposure, household annual income, employment, maternal insurance status, marital status, pre-natal vitamin use and maternal BMI	**BW**: 10-fold ↑ in BDE-17 had sig greatest BW ↑ (12 g) while PBDE 153 sig ↓ in BW (23g) ($p<0.05$)	M
Wu et al. (2010)	China	Case-control; N=153 (128 Guiyu normal births and 25 Chaonan adverse births)	Some women from Guiyu experienced more serious complication during pregnancy, such as anemia, placental abruption, severe pregnancy induced HTN, preeclampsia, prolonged pregnancy, cord around the baby's neck, but the differences between groups were not significant.	UCB BDE-28, -47, -99, -100, -153, -154, -183, -209 and ∑PBDE at delivery (ng/g)	BW at delivery	Not mentioned	A sig difference in medians except for BDE-100, -154, and -209. BDEs median ↑in adverse birth outcome group (LBW, still birth, premature birth) than normal birth group. Median concentration for BDE-28 in the adverse group > compared to the normal birth group (0.686ng/g vs. 0.479ng/g, p=0.016), for BDE-47 (2.24ng/g vs. 1.22ng/g, p=0.004), for BDE-99 (0.865ng/g vs. 0.427ng/g, p=0.001), for BDE-153 it was 0.991ng/g vs. 0.29ng/g (p=0.036)	L
Zhuang et al. (2021)	USA	Prospective longitudinal cohort; N=384	mostly White (62.5%), married (65.6%), and had at least a bachelor's degree (60.1%). The mean infant BW was 3,352 g SD=632 g. The infant sex ratio was roughly 1.18 to 1 (54.2% female to 45.8% male)	PBDE mixture (BDE-28, -47, -99, -100, -153) at 2nd and 3rd trimester	BW at delivery	Cubic-spline gestational age, MA, maternal education, race, marital status, household income, infant sex	**BW**: every 10-fold ↑ in PBDEs mixture ↑ BW by 25 g (95% CI: −18 g, 69 g). In sensitivity analysis, single pollutant PBDE had a non-sig ↑ with BW except for BDE-153 which had a non-sig ↓ BW	H
Preterm birth (n=4)								
Eick et al. (2020)	USA	Prospective longitudinal cohort; N=506	avg MA b/w 25 and 34, majority self identified as Non-Hispanic (NH), White (38.6%) or Hispanic (34%), had a normal pre-pregnancy BMI (47.6%) and one or more prior births (50%). Most women had college degree (22.9%) or graduate education (37.5%).	Maternal serum BDE 47, 99, total PBDE in 2nd trimester	PTB at delivery	MA, maternal race/ethnicity, ppBMI, maternal education, smoking status, parity, and food insecurity	**PTB:** highest tertile BDE-47 (>14.22ng/g lipid) associated with 2.35x ↑ odds of PTB (95% CI: 0.97, 5.72). BDE99 (>4.71 ng/g lipid) associated with 1.25x ↑ odds of PTB (95% CI: 0.55, 2.84). Highest tertile of total BDE (> 18.99ng/g lipid) associated with 2.42x ↑ odds of PTB (95% CI: 1.09, 5.40). adjusted model (OR=1.88, 95% CI: 0.79, 4.48).	M
Peltier et al. (2015)	USA	Case-control; N=73 PTB cases and 65 controls	PTB cases were mainly Caucasian (n=73) and control were mainly African- American (n=132), median age was 27 (range: 18, 41) for PTB and 27 (range: 18, 43) for controls	Maternal plasma BDE-47 at delivery	PTB at delivery	MA, race, and marital status	**PTB:** high (322–1000 pg/ml) PBDE-47 (OR = 3.8, 95% CI: 1.6, 9.7; p = 0.003) or very high (>1000 pg/ml) PBDE-47 (OR = 5.6, 95%CI: 2.2, 15.2; p <0.001) quartile concentrations were at greater ↑ odds of PTB than women with very low levels of BDE-47 (135 pg/ml).	L
Peltier et al. (2021)	USA	Case-cohort; N=184 PTB cases and N=184 controls	PTB avg MA: 31.7 +/- 5.96yrs and non PTB is 30.9 +/-5.20yrs; majority Hispanic descent (around 35-42%), non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, other;	Maternal BDE-47 in first trimester	PTB at delivery	study site, race-ethnicity, infant sex, parity, BMI, gestational diabetes, smoking during pregnancy or placental abruption.	**PTB:** BDE-47 in the fourth quartile (≥4.425 ng/mL) ↑ odds of PTB (adjOR=2.35, 95% CI: 1.31, 4.21)	H
Gao et al. (2016)	China	Cross-sectional; N=125	Avg MA 28.2 ± 5.0yrs, 52% w/h<HS degree, few smoked/used alcohol, ¼ passive smoker during pregnancy, 11.6% worked in factory. Most (71.5%) lived with INC<3000 RMB (< median in Shandong Province); 17.9% resided within 500m of a factory site; 61.4% primiparous, 10.3% took >12 months to conceive, 20.8% previously aborted,	Maternal serum BDE-153 at delivery	PTB at delivery	parental age, maternal education level, parental occupations, mother passive smoke history (during pregnancy), father smoke history (during pregnancy), father alcohol consumption (during	**PTB:** BDE-153 was associated with an ↑ odds of PTB (adjOR=1.05, 95%CI: 1.01, 1.09),	M

			4.8% experienced threatened abortion this pregnancy, 11.1% had an abnormal fetal status, and 2.9% w.h PTB. Few (1.4%) w/h pregnancy complications			pregnancy), mother's BMI, parity and INC		
Fetal growth restriction (n=3)								
Jin et al. (2020a)	China	Case-control; N=293 (98 FGR cases and 195 controls)	Avg MA of FGR cases 29.6 ± 3.9 and control 29.7 ± 3.9 ; avg BW was 2.41 ± 0.46kg & 3.45 ± 0.48kg; ppBMI was 21.24 ± 2.23 kg/m^2 and 21.84 ± 3.07 kg/m^2; majority with HS or < (65% vs. 54%)	Maternal serum and colostrum BDE-207, 208,∑BDE196-209, ∑PBDEs at third trimester	FGR at delivery	GA, maternal education level, annual family income and pregnancy syndrome/ pre-eclampsia	**FGR**: all BDEs ↑ FGR odds in maternal serum and colostrum, In maternal serum, BDE-207 ↑ FGR odds by 4.3% (OR= 1.043 [95%CI: 1.002, 1.087] p=0.042); 1.3% for BDE209 (95%CI: 1.002, 1.024, p=0.025); 0.8% for BDE196-209 (OR= 1.008, 95%CI: 1.001, 1.016, p=0.025) 0.8% for ∑PBDEs (OR= 1.008, 95%CI: 1.001, 1.015, p=0.019) In colostrum, PBDE99 ↑ odds of FGR by 14% (OR=1.142, 95%CI: 1.055,1.236, p=0.001), 3% for BDE153 (OR: 1.030, 95%CI: 1.008, 1.053, p=0.008), 0.6% for BDE17-153 (OR: 1.006, 95%CI: 1.000,1.011, p=0.036), 0.6% for ∑PBDEs (OR: 1.006, 95%CI: 1.000, 1.011, p=0.037).	M
Jin et al. (2020b)	China	Case-control; N=202 (101 FGR and 101 healthy newborns.)	Avg age 27.8 ± 4.3 years; majority had HS degree or < (67%); majority also had INC>5000 (60%); few w/h pregnancy syndrome (26%); Av113hineaf FGR cases were (2.29 ± 0.43) which were significantly lower than those of the controls (3.31 ± 0.34) kg .	Maternal serum BDE-17, 47, 66, 153, 207, 208, 209, ∑19PBDEs at third trimester	FGR at delivery	GA, education, income, and pregnancy syndrome	**FGR:** ***Crude analysis:*** BDE-17 non-sig ↑ odds of FGR (OR = 1.21, 95% CI: 0.87, 1.67, p=0.254), BDE-47 sig ↑ odds of FGR (OR = 1.13, 95% CI: 0.92, 1.38, p=0.249) BDE-66 sig ↑ odds of FGR (OR = 1.16, 95% CI: 0.98, 1.39, p=0.087), BDE-153 sig ↑ odds of FGR (OR = 1.12, 95% CI: 0.98, 1.27,, p=0.089. ***Adjusted analysis:*** A unit ↑ in BDE-207 had the highest and sig ↑ odds of FGR (OR = 1.10, 95% CI: 1.02,1.19, p=0.016) and ∑BDE(19) showed sig ↑ odds of FGR (OR=1.01, 95%CI: 1.00, 1.02, p=0.037).	M
Zhao et al. (2019)	China	Case-control; N=260 (130 FGR cases and 130 healthy controls)	Avg MA 27.94 ± 4.47 years; GWG 12.68 ± 4.14 kg; ppBMI 20.30 ± 2.93 kg/m^2; most w/h college degree (36.95%); <5000 RMB (47.39%); had pregnancy complication (30.92%); passive smoker (42.15%);	Maternal serum & UCB 13 lower BDE brominated (BDE-17, −28, –33, −47, −49, −66, −99, −100, −138, −153, −154, −183, −190, −196, −203, −206, −207, −208, and −209) & 6 higher BDE (BDE-196–209) at 24, 28, and 32 weeks of gestation.	FGR at delivery	GA, GWG, and ppBMI	**FGR:** every log-unit (10-fold) ↑ in BDE-206, BDE-17–190, BDE-196–209 and ∑19PBDEs was associated with 56.9% (OR = 1.569, 95% CI: 1.053, 2.338), 186.0% (OR = 2.860, 95% CI: 1.233, 6.634) 68.8% (OR = 1.688; 95% CI, 1.024 to 2.783) and 138.7% (OR = 2.387, 95% CI:1.220, 4.668) ↑ odds of FGR .	M

Apgar score (n=3)								
Tan et al. (2009)	Singapore	Cross-sectional; N=41	Avg MA 31+/- 5.6 years; GWG 14.3 +/- 7.28kg; ppBMI was 23.6+/-5.55 kg/m^2; closely primiparous 0.683+/0.65 parity; wer114hinesese (46.3%), Indian (22%), Malay (26.8%) and other (4.9%); mostly career women (65.9%) and rest housewives; <5% smokers & alcohol users; mostly male (58.5%); Apgar score at 1min was 8.49+/-0.312	UCB BDE-47 and 99 at delivery	Apgar score at delivery	None described	**Apgar scores** at 1min post-birth and found a positive association with neonatal performance in correlation to detectable PBDE-47 (estimated β = 0.21, 95% CI: 0.18-0.24) and detectable PBDE-99 (estimated β =0.15, 95% CI: 0.05-0.25).	L
Wu et al. (2010)	China	Cross-sectional; N=153 (Guiyu (N= 102) and Chaonan (N=51))	Median concentration of PBDE in Guiyu group (13.84 ng/g) vs. Chaonan group (5.226 ng/g)	UCB BDE-28, -47, -99, -100, -153, -154, -183, -209 and ∑PBDE at delivery	Apgar score at delivery	None described	**Apgar scores** from Guiyu (PBDE exposed group) (9.71±2.10) < than Chaoan (control group)(10.00±0.00) (t= -3.372; p=0.001)	L
Xu et al. (2013)	China	Cross-sectional; N=154 (101 from Guiyu and 53 from Chaonan)	Avg MA in Guiyu and Chaonan were 26.20+/-3.36 and 26.72+/-3.87yrs; both had majority with senior HS education (70.3% & 64.2%); mean Apgar were 9.80+/-0.40 & 10.00+/-0.00	UCB BDE-28, 47, 99, 100, 153, 154, 183, 209 at delivery	Apgar score at delivery	None described	**Apgar scores** in Guiyu (PBDE exposed group)(9.80± 0.40) were < than Chaonan (control group)(10.00±0.00)(p=0.002)	L

Abbreviations: Post-secondary education [PSE], low education attainment [LEA]; High school [HS]; free thyroxine [ft4]; total thyroxine [TT4]; thyroid stimulating hormone [TSH]; umbilical cord blood [UCB]; gestational age [GA]; Maternal age [MA]; maternal weight gain [MWG]; smoking status [SS]; delivery [DEL]; body mass index [BMI]; Pre-pregnancy body mass index [ppBMI]

Table 8: Summary table of studies on PBDE and Biomarker hormone effects (N=18)

Authors	Country	Study design & sample size	Population characteristic	Exposure	Outcome	Trimester (outcome measurement)	covariates	Findings (Beta coefficient /OR/RR)	NOS Quality
Thyroid hormones (N=16)									
Abdelouahab et al. (2013)	Canada	Prospective longitudinal cohort; N= 260	avg MA: 28.1+/-4.5 years, multiparous (69%), highly educated (> 12yrs of PSE). At recruitment, 18% obese (BMI>30; 360 women). SS differed at recruitment and delivery	1st trimester maternal serum and UCB at delivery PBDE-47, -99 and ΣPBDE	1st trimester maternal serum TSH, TT3, TT4, FT3, FT4 at recruitment, Serum TSH, TT3, TT4, FT3, FT4 at delivery & UCB TSH, TT3, TT4, FT4 at delivery. Subclinical hypothyroidism ((normal FT4 level (11.5–22.7 pmol/L) and TSH level >2.5 mIU/L))	1st (<20 wks), delivery	total T3: GA, MA selenium, BMI, and/or not PCB-153	Overall, ↓maternal FT4 & TT4 (at recruitment + DEL) & ↓UCB TT3. At recruitment, lipid models ↓ FT4 and TT3 & ↑ FT4 ($p<0.05$) **TT4**: For every unit ↑ in PBDE-47 (β=-0.29, 95% CI: −0.51, −0.08), PBDE-99 (β=-0.35, 95% CI: −0.57, −0.12) and ΣPBDE (β = -0.36, 95%CI: −0.56, −0.13), TT4 ↓ by 0.29, 0.35 and 0.36ng/g lipid. **TT3**: After adjustment for every unit ↑ in PBDE 47 and PBDE-99, ↓ TT3 by 7.81ng/g lipid (95% CI:−11.37, −4.26) and 4.19ng/g lipid (95% CI: −8.26, −0.12). After stratifying the lipid vs. volume-based model, similar results were seen with ↓ TT3.	H
Chevrier et al. (2010)	USA	Cross-sectional; N=270	avg MA: 25.5+/-5 years, low income, LEA (HS degree), 95% Latina emigrated from Mexico within 10 yrs at time of enrollment (75%), multiparous (67%), Few smoker/alcohol user, most (61%) overweight/ obese before pregnancy	Maternal serum PBDE-28, -47, -99, -100, -153, and Σ4 PBDEs (47, 99, 100, and 153) in 2nd trimester	fT4, TT4,TSH and subclinical hyperthyroidism (↓TSH and ↑FT4) in 2nd trimester	3rd	MA, GA, ppBMI, parity, SS, infant gender, method of delivery,	**TSH**: All BDEs had sig ↓TSH ($p<0.05$) where BDE100 had the highest (β= -0.09, 95% CI: –0.15,–0.02) $p<0.01$) **TT4**: No association with any BDE and TT4 All BDEs except for BDE-28 had non-significant ↓ TT4 BDE-100, BDE-153 & ΣPBDEs sig ↑ odds of subclinical hyperthyroidism	M
Chevrier et al. (2011)	USA	Prospective longitudinal cohort; N=289	avg MA: 25.1 years, low-income, mainly Latina, Mexican born & no HS degree, >obese (BMI=30) before pregnancy, & about 1/4 gave birth by spontaneous unassisted vaginal delivery.	3rd trimester and at delivery PBDE-47, -85, -99, -100, -153 and ΣPBDE	Dried blood spot TSH at delivery	First (<20wks), delivery	OR model: infant age at time of heel stick for TSH measurement, BW, sex, and duration of gestation	**TSH**: All BDEs had no or weak, non-sig ↓ TSH in unadjusted models but after covariates adjustment, association came closer to null BDE153 had a non-sig decreased odds of TSH (OR= 0.75, 95% CI: 0.36, 1.56)	M
Ding et al. (2017)	China	Cross-sectional; N=123	avg MA: 28.2+/- 5.0 years, 64.2% primiparous & almost 49.6% w/h HS degree or more. Most (91.1%) lived w/h monthly income < RMB (¥) 5000 yuan. 52.8% had normal BMI before pregnancy. One-third (34.1%) lived w/h a smoker during pregnancy, few smokers/alcohol users, resided for at least 3yrs in the area	UCB PBDE-47, -99, -100, -153, Σ4PBDE (BDEs 47, 99, 100, & 153) at delivery	UCB TSH, fT3, T3, fT4, T4 at delivery	delivery	MA, ppBMI, parity, smoking status, infant gender, method of delivery, and GA	**TT4**: BDE-99 and Σ4 PBDEs associated with a 0.41 µg/dL (95%CI: 0.10 to 0.72, $p<0.05$) and 0.37 µg/dL (95% CI: 0.06 to 0.68, $p<0.05$) ↑ in TT4	M
Herbstan et al. (2008)	USA	Cross-sectional; N=289	median MA: 25 years (14–43). ⅓ no HS degree,⅓ at least 1 year of college. Most black (72%), 21% white, and 7% Asian. Approximately 41% of mothers delivered first child, and 19% active smokers during pregnancy. About 48% ppBMI as overweight or obese.	UCB PBDE 47, 100, 153 at delivery	UCB TSH, T4 and FT4 at delivery	delivery	baby's sex, GA, MA, maternal race, maternal ppBMI SS, and history of STDs	**TSH**: BDE-47 sig ↓ odds of high TSH **TT4 & FT4:** BDE-100 ↑ odds of low TT4 , & BDE-153 ↑ odds of low TT4 and FT4 (data not shown)	H

Kim et al.(2009)	Korea	Cross-sectional; N=108	MA range from 20 to 42 years and ppBMI was 21.23 ± 4.57 kg/m^2. Avg pregnancy period was 39.28 ± 1.71 wk (range 31.4–41.4 wks). The mean infant BW (g), height (cm), and HC (cm) were 3153.43 ± 575.05 (range 1885–4430), 49.01 ± 2.67 (range 38–54), and 33.80 ± 3.47 (range 30.30–37.51),	UCB of individual and ΣPBDE (BDE-28, BDE-47, BDE-99, and BDE-100))	UCB T4 and TSH	Delivery	None described	**TSH & T4**: No sig association with individual BDEs and T4. No association with ΣPBDE and TSH or T4	L
Kim et al. (2013)	Korea	Cross-sectional; N=105	Avg MA: 33+/-4 years, half primipara, most w/h normal ppBMI (22.1+/- 10kg/m^2)	Maternal serum BDE47, Σ19 PBDE (17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119,126, 138, 153,154, 156, 183, 184 * 191)	Maternal fT3, T3, fT4, T4, TSH	delivery	MA, GA, mode of delivery, parity, and ppBMI	**TT3**: BDE-47 sig ↓ TT3 (β = -0.042, 95% CI= -0.084, -0.000), ΣPBDE ↓ TT3 (β = -0.112, 95% CI: 0.170, -0.054) **FT3**: ΣPBDE ↓ FT3 (β = -0.049, 95% CI: -0.088, 0.009) **TT4**: BDE47 sig ↑ odds of low TT4 (OR=1.35, 95% CI: 1.07, 1.71).	M
Kim et al. (2015)	Korea	Cross-sectional; N=104	Avg MA: 33.3 ± 3.9 years, 50% primiparae. ⅔ gave birth to babies by spontaneous vaginal delivery. ppBMI mostly within normal weight range,(21.8 kg/m^2)	UCB BDE47, Σ19 PBDE (17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119,126, 138, 153,154, 156, 183, 184, 191) at delivery	UCB FT3, TT3, FT4, TT4, TSH (2 day post partum therefore not considering) at delivery	delivery	MA, GA, mode of delivery, parity, ppBMI, SS during pregnancy and MWG during pregnancy	No association with Σ19 PBDE and any THs except for TSH **TSH**: BDE-47 ↑ bloodspot TSH (β = 0.327, 95% CI: 0.03, 0.62)) and BDE-99 and ↑ cord TSH (β = 0.211, 95% CI: 0.00, 0.42))	M
Lignell et al. (2016)	Korea	Cross-sectional; N=220	Median age: 28 years(18–41); ppBMI: 23 kg/m^2 (18–44); MWG: 22g (3.9–46); 95% from Nordic country; 49% ≤4yrs of HS; first-time mothers	Breast milk BDE-153 at delivery	Maternal FT4, TT3, TSH in 1st and 3rd trimester	1st and 3rd trimester, 3wks & 3 months after birth	MA, ppBMI, smoking during pregnancy, season of sampling during pregnancy. MWG only added to 3rd trimester model	**T3, FT4, T SH**: BDE-153 sig ↓ 1st trimester T3 (β = −0.25, SE = 0.07, p = 0.001)), ↓ FT4 (non sig) and ↓ TSH (non sign) No association with BDE-153 and 3rd trimester THs	H
Lin et al. (2011)	China	Prospective longitudinal cohort; N=54	MA and ppBMI were 30.6 ± 5.01 years (median = 31.0 yr) and 23.2 ± 4.53 kg/m^2 (median = 21.8 kg/m^2). GA of newborns ranged from 36 to 40 weeks, with the mean of 38.5 wks.	UCB BDE-15, 28, 47, 99, 100, 153, 154, and 183 at delivery	Cord blood T3, T4, TSH, FT3, and FT4 at delivery	delivery	maternal age, pre-pregnant BMI and gestational age.	**T3**: BDE-99 (r = −0.327, p = 0.017), BDE-154 (r = −0.314, p = 0.022), and BDE-183 (r = −0.271, p = 0.049) ↓ T3 **FT3**: BDE-99 (r = −0.384, p = 0.005), BDE-154 (r = −0.305, p = 0.026), BDE-183 (r = −0.271, p = 0.049), and PBDEs (r = −0.281, p = 0.041) ↓ FT3 **FT4**: Levels of BDE-99 (r = −0.342, p = 0.012) and BDE-183 (r = −0.273, p = 0.048) ↓ FT4. BDE-99 ↓ FT4 × TSH (r = −0.284, p = 0.039). **FT4/T3**: BDE-100 (r = 0.352, p = 0.010), BDE-154 (r = 0.414, p = 0.002), and BDE-183 (r = 0.306, p = 0.026) ↑ FT4/T3. BDE-47 and BDE-153 had no correlation association with TH	M
Lv et al (2015)	China	Cross-sectional; N=64	Avg MA at delivery 28.8±5.3 years; ppBMI 21.8 kg/m^2; 51.6% Primipara; 67.2% had ≤ 9yrs of education; 60.9% had a maternal occupation of housewife; baby mean apgar score: 9.9±0.5; avg BW: 3276±477.9; avg BL: 49.9±1.4	Maternal adipose-serum BDE-28, 47, 99, 100, 153, 154, 183, 209, sumPBDE7 and sumPBDE8 (including BDE-209) at delivery	Maternal FT3, FT4, TT3, TT4, TSH at delivery	1–3 days before delivery	MA, ppBMI, gestational weeks, and maternal parity	**FT4**: BDE28 & BDE209 had non sig ↓ FT4. **TT4**: Only BDE-154), BDE-153, BDE183, BDE-209 had non-sig, ↓TT4 **FT3**: BDE-99 and BDE-209 non-sig ↓ FT3 **TT3**: BDE-209 non-sig ↓TT3 **TSH**: BDE-154, -153, -183 non-sig ↓ TSH. Other PBDEs had non sig ↑ TT3, TT4, FT3	H
Miranda et al (2015)	China	Cross-sectional; N=136	Avg age 23+/- 4 years predominantly low-income, non-Hispanic black women.	Maternal BDE138/158, 153, 170, 180, and ΣPBDE in third trimester	FT4 TT4, FT3 TT3, and TSH in third trimester	3rd	infant sex, parity, and MA, race, educational attainment and smoking status.	No association with any THs (data not shown)	M

Stapleton et al. (2011)	UK	Prospective longitudinal Cohort; N=136	Non-Hispanic black b/w ages 18-39, first time mothers, >87% completed HS degree. One women reported a personal history with thyroid problems and was not excluded from this study	Maternal PBDE 47, 99, 100, 153, and 209, ΣPBDE, three phenolic metabolites (i.e., containing an –OH moiety) at third trimester (35–36 weeks)	TSH, FT3, TT3, FT4, TT4 in third trimester	3rd	SS, maternal race, MA, gestational age at blood draw, and parity	**TT4**: BDEs 47, 99, & 100 sig ↑ odds TT4, (r = 0.32–0.50,p < 0.05). **FT4**: BDE-47, -153, ΣPBDE, ↑ odds FT4 **T4**: A 2-fold ↑ PBDE had a 1.42 times [95% CI: 1.08– 1.86, p = 0.01] for BDE-47; 1.37 times (95% CI, 1.01–1.84, p = 0.04) for BDE-100; 1.25 (95% CI, 1.00–1.57, p = 0.05) for BDE-99; and 1.45 times (95% CI, 1.04–2.01, p = 0.03) for ∑BDEs ↑ odds for normal vs. low or high vs. normal T4. **FT4**: 2-fold ↑ in BDE-47, ↓ low FT4 odds by 40% (OR= 0.60; 95% CI: 0.39– 0.93, p= 0.02) & 49% for ΣBDEs (OR= 0.51; 95%CI: 0.27–0.97, p= 0.04)	M
Vuong et al.(2015)	USA	Prospective longitudinal cohort; N=443 (maternal serum (n=187) & cord serum (n= 256))	most gave birth to babies by spontaneous, vaginal delivery	Maternal PBDE 28, 47, 99, 100, 153, ∑PBDEs at 2nd trimester	Maternal serum in 2nd trimester or UCB at delivery T3, T4, FT3, FT4, TT3, TT4, TSH and TH antibody (TgAb or TPOAb)	second trimester (16 ± 3 weeks of gestation) and delivery	MA, race/ethnicity, education, parity, family income, SS, alcohol consumption, GA at serum collection, & total serum PCB concentrations	**TT3:** BDE-47 sig ↑ TT3 (β = 8.71 ng/dL; 95% CI: 0.42, 16.99) **TT4:** BDEs 28 and -47 sig ↑ TT4 (β = 0.85 µg/dL; 95% CI: 0.05, 1.64; β = 0.82 µg/dL; 95% CI: 0.12, 1.51) **FT3:** 10 fold ↑ BDE-47 and -28 sig ↑ FT3 (β = 0.14 pg/mL;95% CI: 0.02, 0.26 and β = 0.12 pg/mL; 95% CI: 0.01, 0.22) and **FT4**: ↑ BDE-47 and -28 sig ↑ FT4 by 7% (95% CI: 1%, 13%) and 6% (95% CI: 1%, 10%), **FT3**: No association with PBDE and cord TH except BDE-28 which ↓ mean of FT3 by 6% (95% CI: –12%, –0.2%)	H
Zhang et al. (2010)	China	Cross-sectional; N= 50 (25 from Zone A and 25 from Zone B)	Mean MA at delivery (mean: 26 years, range: 19-36 for zone A, mean: 27, range: 22-38 for zone B), habitation year in local area (mean: 7.2, range: 5-36 for zone A, mean : 9.1, range: 5-38 for zone B) and baby BW (mean: 3.3 Kg, range: 2.7-4.0 Kg for zone A, mean : 3.4 Kg, range: 2.6-4.1 Kg for zone B), length (mean: 49.5, range: 45-52 cm for zone A, mean : 50.0, range: 48-55 cm for zone B), neonate sex were not statistically sig b/w two groups (p > 0.05). The newborns were healthy with Apgar scores all 10 except one newborn baby (Apgar scores = 6) in zone A and all 10 in zone B which was not statistically significant (p = 0.34).	UCB ∑PBDE at delivery	Maternal TT3, TT4 and TSH at 2nd trimester	2nd	None mentioned	**TT4:** ∑PBDE concentrations in zone A (median: 23.43 pg/g) had sig lower TT4 (median: 112.47nmol/L, 95% CI: 62.90-172.10) as compared to zone B (median:16.15 pg/g) TT4 levels (median: 138.96 nmol/L, 95% CI: 80.48-208.74) (t-test p value: 0.015) **TSH:** ∑PBDE concentrations in zone A (median: 23.43 pg/g) had sig lower TSH (median: 1.15nmol/L, 95% CI: 0.50-11.79) as compared to the zone B (median:16.15 pg/g) TSH levels (median: 2.65 nmol/L, 95% CI: 0.28-11.80) (t-test p value: 0.015) **TT3:** ∑PBDE has non sig difference in zone A compared to zone B, however zone A had ↓ TT3 compared to zone B	M
Zota et al. (2011)	USA	Cross-sectional; N=25	Avg age: 23 ± 7.3 years, 84% were <30 years of age. Majority of women were born in the US but were an ethnically diverse community from an Asian and European descent.	Maternal PBDE 28, 47, 85, 99, 100, 153, 207, ΣPBDE5 in 2nd trimester	Maternal TSH, TT4, FT4 in 2nd trimester	2nd	TSH model: insurance type and lipids, TT4: additionally for age	**FT4**: BDE-28 marginally sig ↓ FT4 (β = -0.11, 95% CI: -0.24, 0.02, p<0.10), PBDE & FT4 & TT4 relation were weak, inconsistent, & non sig. **T SH:** ΣPBDE5, BDE-47, & BDE-85 non sig ↑TSH, BDE-207 non sig ↓TSH	M

Reproductive hormones (n=1)									
Gao et al. (2016)	China	Prospective longitudinal cohort; N=125	Avg age 28.2 ± 5.0 years, 52% w/h<HS degree, Few smoked/used alcohol, 1/4 exposed to passive smoke during pregnancy, 11.6% worked in a factory. Most (71.5%) lived with INC<3000 RMB (below median in Shandong Province); 17.9% resided within 500m of a factory site; 61.4% primiparous, 10.3% took >12 months to conceive, 20.8% previously aborted, 4.8% experienced threatened abortion this pregnancy, 11.1% had an abnormal fetal status, and 2.9% w.h PTB. Few (1.4%) w/h pregnancy complications	Maternal serum BDE- 28, -47, 85, -99, -100, -153, -154, -183 &∑ 5 PBDEs (BDE-28, -47, -85, -99, -100, -153, &-183) at delivery	Maternal E2, T, LH, FSH at delivery	delivery	MA, maternal education level, maternal occupations, mother passive smoke history, mother's BMI, parity and family income.	**FSH**: BDE-47, BDE-100, & ∑ 5 PBDE ↓ FSH. A log unit ↑in BDE-47 ↓ FSH by 1.19 IU/L (95% CI: −1.32, −1.02), 1.17 IU/L (95% CI: −1.36, −1.01) for BDE100 and sig ↓in 1.26 IU/L (95% CI: −1.55, −1.02) for ∑ 5 PBDEs. **E2, T, or LH**: No association w/h E2, T, or LH; inconsistent direction of association.	M
Inflammatory biomarkers (n=1)									
Zota et al. (2018)	USA	Cross-sectional; N=103	majority (58.3%) had BMI ≥30 kg/m^2, 86.4% had a college degree or less; 54.6% had >federal poverty income 34% are 18-25yrs, 34.3% African American, 13.7& White, 32.4% Latina, and 19.6% other descent	Maternal serum 47, 99, 100, 153 and ∑PBDE in 2nd trimester	IL-6,IL-10, TNF-α, LTL in 2nd trimester	2nd	MA, race/ethnicity, time varying BMI, parity, education, SS, gestational weeks at baseline, and visit.	All BDEs ↑ TNF-α, IL-6, & IL-10. **IL-6:** Unit double of ∑ PBDE, IL-6 ↑ by 15.26% (95% CI: 1.24, 31.22) **TNF-*α***: Unit double of ∑ PBDE , TNF-a ↑ by 3.74% (95% CI: −0.19, 7.82). **IL-10:** Only BDE100 showed ↓ w/h IL-10 (β = -2.21 (-8.91, 4.99); **LTL**: BDE153 had small, sig ↑LTL, among obese not among overweight women	H

Abbreviations:Post-secondary education [PSE], High school [HS]; free thyroxine [ft4]; total thyroxine [TT4]; thyroid stimulating hormone [TSH]; umbilical cord blood [UCB]; gestational age [GA]; maternal age [MA]; maternal weight gain [MWG]; smoking status [SS]; delivery [DEL]; body mass index [BMI]; pre-pregnancy body mass index [ppBMI]; Luteinizing hormone [LH]; Testosterone [T]; follicle stimulating hormone [FSH]; estradiol [E2]

Table 9: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 68
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 64
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 65
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 73
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 71
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix Table 1-4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 73
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 73
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	N/A
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 74
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 74
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Figure 5

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 75
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 5
Study characteristics	17	Cite each included study and present its characteristics.	Appendix Table 6-8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix Table 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendix Table 6-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix Table 6-8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 80-87 & Appendix Table 6-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 112
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A

DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 100-110
	23b	Discuss any limitations of the evidence included in the review.	Page 111
	23c	Discuss any limitations of the review processes used.	Page 112
	23d	Discuss implications of the results for practice, policy, and future research.	Page 116
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	Page 119
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A