

# How microplastic components influence the immune system and impact on children health: Focus on cancer

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## Abstract

**Background:** As a result of human socioeconomic activity, industrial wastes have increased distressingly. Plastic pollution is globally distributed across the world due to its properties of buoyancy and durability. A big health hazard is the sorption of toxicants to plastic while traveling through the environment. Two broad classes of plastic-related chemicals are of critical concern for human health—bisphenols and phthalates. Bisphenol A (BPA) is an endocrine-disruptor compound (EDC) with estrogenic activity. It is used in the production of materials that are used daily. The endocrine modulating activity of BPA and its effects on reproductive health has been widely studied. BPA also has effects on the immune system; however, they are poorly investigated and the available data are inconclusive. Phthalates are also EDCs used as plasticizers in a wide array of daily-use products. Since these compounds are not covalently bound to the plastic matrix, they easily leach out from it, leading to high human exposure. These compounds exert several cell effects through modulating different endocrine pathways, such as estrogen, androgen, peroxisome proliferator-activated receptor gamma, and arylhydrocarbon receptor pathways. The exposure to both classes of plastic derivatives during critical periods has detrimental effects on human health.

**Methods:** In this review, we have compiled the most important of their perinatal effects on the function of the immune system and their relationship to the development of different types of cancer.

**Results/Conclusion:** The administration of bisphenols and phthalates during critical stages of development affects important immune system components, and the immune function; which might be related to the development of different diseases including cancer.

## KEY WORDS

bisphenol A, cancer and critical periods of development, immune system, phthalates

## 1 | INTRODUCTION

### 1.1 | Environmental pollution and its impact on organisms

As a result of human socioeconomic activity, industrial wastes have increased alarmingly. All pollutants have direct and indirect effects in almost every ecosystem. No matter what their impact is, pollution affects every species on this planet. Wildlife is prone to suffer the same symptoms and diseases suffered by humans (Lovett et al., 2009). Global warming is changing some ecosystems faster than the capability of animals and plants to adapt, leading to possible extinction of a huge number of species (Andrady, Aucamp, & Austin, 2016). Toxicity of the water, reduced oxygen concentration in deeper layers of bodies of water and difficulty in adapting to the new substances may damage indigenous fauna and flora in several ways. Among the worst and most widespread contaminants in the environment are plastics (Bellard, Bertelsmeier, Leadley, Thuiller, & Courchamp, 2012).

## 2 | THE PROBLEM

Plastics have great practical value, and this has allowed them to be readily accepted by the consumer society to the point that they are now present in many of the everyday products we use. Part of the success of plastic materials is that they are inexpensive, light, and resistant. However, their resistance to corrosion and degradation makes them slow to decompose, leading to a great environmental problem (Hammer, Kraak, & Parsons, 2012). It was believed that plastics did not react with anything, that is, that they were stable, inert and therefore did not contaminate; that is not true. Unfortunately, plastics make up between 60 and 80% of the litter present in the marine environment. The wind acts on the surface of seas and oceans, acting as the engine to spread litter over these waters. The currents or turns manage to collect all kinds of garbage in their path and finally form what are known as garbage islands or plastic islands (Sharma & Chatterjee, 2017).

## 3 | PLASTIC ISLANDS FORMATION

These plastic islands contain waste of all kinds, sizes and different materials; but plastic is its biggest component. What especially stands out are the millions of tiny pieces of plastic, some the size of a grain of rice known as microplastics. In addition, marine currents, also known

as ocean turns, along with winds and atmospheric pressure, produce a circulation that encompasses floating debris (mainly plastic) and hold them together in plastic islands (Sharma & Chatterjee, 2017). The debris concentrated in the different plastic islands becomes a whirlpool (Ekman Spiral) stimulated by sea currents and wind circulation; this prevents them from dispersing toward the coast and causes the smallest and finest particles to go to the bottom of the sea or ocean. As for the location of the different plastic islands that exist in our oceans, these coincide with the oceanic turns; they can be classified in five different types: the North Atlantic Turn, the South Atlantic Turn, the Indian Ocean Turn, North Pacific Turn, and the South Pacific Turn (Jambeck et al., 2015).

The largest of these plastic islands are located in the Pacific Ocean; two in the Atlantic; one in the Indian Ocean; and two smaller ones in the Mediterranean Sea and the other in the Caribbean Sea. The largest of the plastic islands, in the North Pacific Ocean, located about 1,000 km from Hawaii. It contains an estimated 1.8 billion pieces of plastic. It weighs around 80,000 tons and covers an area of approximately 1.6 million square kilometers. The plastic island of the South Pacific, located in the South Pacific Ocean, between Australia and South America, is estimated to have an area of  $2.6 \text{ km}^2$  (approximately the size of Iran) and a density of around 390,000 particles per square mile in the center of the island. The precise measurements of the plastic island of the North Atlantic Ocean, located from the Equator to Iceland, the North America, Europe and Africa is unknown. It probably has a particle density of about 7,220 pieces per square kilometer. The plastic island of the South Atlantic is found in the southern portion of the Atlantic Ocean, and is quite small compared to the others. It covers approximately  $715,000 \text{ km}^2$ . It has a particular density of 40,000 pieces per kilometer and contains about 2,860 tons of plastic. The plastic island of the Indian Ocean can be seen over the Indian Ocean. Due to its remote location, this plastic island is difficult to study, but its size is estimated at 2.1 million square kilometers (Lebreton et al., 2018). The plastic island of the Caribbean located at approximately  $21^\circ$  North latitude and  $65^\circ$  West longitude, off the coast of Belize, and Cuba. There are not many studies on the Mediterranean Sea, but an accumulation of plastics with an extension close to  $900 \text{ km}^2$  has been detected near the island of Elba (Italy), and it is estimated that this sea has some 3.5 million tons of plastic in total (Lebreton et al., 2018). It is important to consider that the size of them varies with each cyclonic season; thus, it is clear that plastics and microplastics are a huge problem around the world and a huge threat to humanity. In Figure 1 are depicted some of the so-called "plastic islands" that make for worldwide dismal landscapes.



**FIGURE 1** Photograph of several plastic islands formed in seas and oceans. These plastic islands contain waste of all kinds, sizes, and different materials; but plastic is the biggest component. Notable are the millions of tiny pieces of plastic, some the size of a grain of rice known as microplastics. In addition, marine currents, also known as ocean turns, along with winds and atmospheric pressure, produce a circulation that encompasses floating debris (mainly plastic) and holds them together in bodies of water to create these plastic islands

Once microplastics enter the marine food web, there is a strong possibility that it will contaminate the human food chain as well, through a process called bioaccumulation, where chemicals from the plastics enter into the body of the animal when it is feeding on the plastic. Then, it is consumed by the prey and the chemicals pass to the predator—making their way up the food web that includes humans, leading to the development of multiple diseases for wildlife and humans (Hammer et al., 2012; Sharma & Chatterjee, 2017).

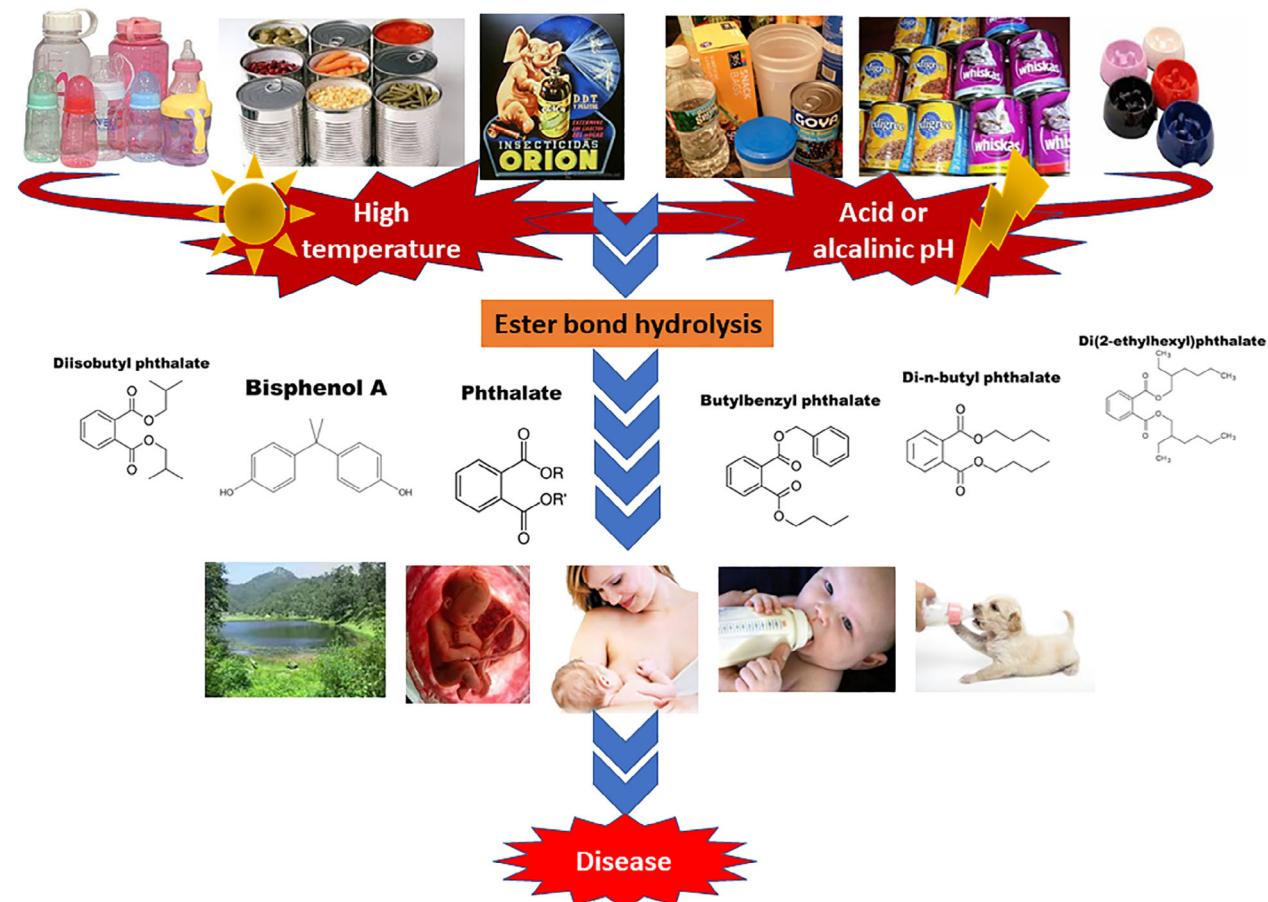
Thus, the present review will discuss the effects of this exposure to microplastic materials in preclinical studies with a single administration or with exposures restricted to different stages during the life of different organisms, including humans, that affects the function of the immune system, and how can they involved in the promotion of the development of different types of cancers. Nowadays, the term environmental pollutant can be properly applied to plastic derivatives such as bisphenols and phthalates which also have detrimental health effects (Meeker, Sathyannarayana, & Swan, 2009; Schmidt, 2012). Animal studies have shown that low exposures of EDC during the perinatal period can result in developmental abnormalities as well as neurological, metabolic, reproductive, or carcinogenic effects in the offspring (Fenton, Reed, & Newbold, 2012; Rachon, 2015).

## 4 | PERINATAL STAGE OF DEVELOPMENT

First, we would define the two periods of development that will be discussed. The perinatal period is defined as the time span from Week 28 of gestation to the seventh day of postnatal life, while, the neonatal period refers to the first 28 days of the newborn's life. Both of them are considered as critical periods of the development or windows of susceptibility, because exposure to any chemical or biological stimuli, among others, impact on the development and proliferation of different types of cells of the new individual (Figure 2) (Terry et al., 2019; Waterland & Michels, 2007).

## 5 | BPA AND PHTHALATES

BPA is the most studied compound of the bisphenol family; however, several of its structural analogs have also recently been considered. In the case of phthalates, various compounds such as diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP) have been associated with side effects on health. Both kinds of microplastic derivatives are found in food packaging and personal care/household products and they have affinity for estrogen receptors (ERs) for which

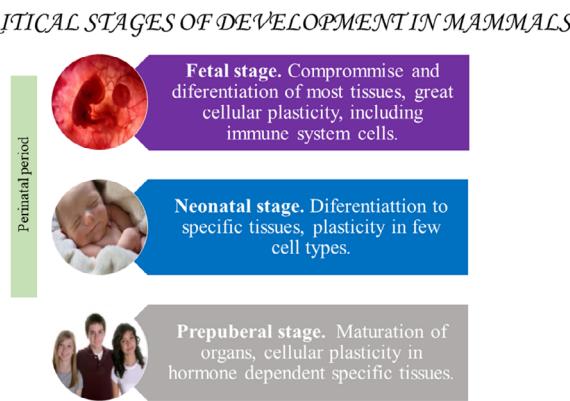


**FIGURE 2** Bisphenol A (BPA) and phthalates are endocrine disruptors. An endocrine disrupting compound (EDC) is defined as an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the organism, and are responsible for homeostasis, reproduction, and developmental processes. EDCs mimic endogenous hormones and bind to their receptors inducing functional and regulatory activities of gene expression. Two broad classes of microplastics-related chemicals are of critical concern for human health BPA and additives used in the synthesis of plastics which are known as phthalates. Microplastics are polymers, long chains of molecules usually made of carbon, hydrogen, oxygen, and/or silicon, which are chemically linked together or polymerized. Different polymer chains can be used to create forms of plastics with unique and useful properties. BPA is a basic building block of polycarbonate plastics, such as those used for bottled water, food packaging, and other items. While it has been considered benign in the form of a heavily cross-linked polymer, its bonds can break down over time, when plastics are repeatedly washed, exposed to heat or other stresses, liberating the building blocks of the chemical, which are toxic. Adding to the health risks associated with BPA is the fact that other ingredients—such as plasticizers—are commonly added to plastics. Many of these potentially toxic components also can leach out over time. Among the most common is a chemical known as diethylhexyl phthalate (DEHP). In some products, notably medical devices including IV bags or tubing, additives like DEHP can make up 40 or 50% of the product. Both BPA and DEHP are classified as endocrine disruptors

they receive the name of EDCs (Figure 3) (Almeida, Raposo, Almeida-González, & Carrascosa, 2018; Del Pup et al., 2016; Schettler, 2006).

BPA can be released easily from these materials due to incomplete polymerization or hydrolysis of the polymers that contain it, which can occur when they are exposed to high temperatures, acidic conditions, or enzymatic processes (Figure 3). The main BPA exposure source in animals and humans is through intake of food and beverages that have been in contact with materials manufactured with this compound, which detaches from

its matrix and is ingested orally (Figure 3) (Almeida et al., 2018). BPA is classified as an EDC with estrogenic characteristic since it can bind to nuclear ER $\alpha$  and ER beta (ER $\beta$ ) and trigger signaling pathways, even when its affinity is lower (<1,000) than the endogenous ligand, 17 $\beta$ -estradiol (Kim & Park, 2019). In addition, BPA also binds to the estrogen like G-coupled protein receptor, the estrogen-related receptor gamma, the arylhydrocarbon receptor, the thyroid hormone receptor, the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), the glucocorticoid receptor and the (Rezg, El-Fazaa, Gharbi, &



**FIGURE 3** Critical stages of development. The gestational period is the time that the fetus spends inside the mother, while the neonatal period refers to the first days of the newborn's life. Both, gestational and neonatal periods, are the so-called perinatal period that is defined as the time span from Week 28 of gestation to the seventh day of life outside the womb. Both of them are considered as critical periods of development or windows of susceptibility, because exposure to any chemical or biological stimuli, among others, impacts the development and proliferation of immune and epidermal cells of the new individual

Mornagui, 2014; Seachrist et al., 2016). Despite the fact that the Food and Drug Administration and the European Food Safety Agency calculated that the tolerable daily intake of BPA is 50 µg/kg/day, it has been estimated that BPA exposure via food packaging is 0.185 µg/kg/day in adults and up to 2.42 µg/kg/day in children from 1 to 2 months of age (Seachrist et al., 2016). Notably, it has been demonstrated that exposure of BPA at the tolerable concentrations or below is related to negative effects on the health of both humans and rodents (Konieczna, Rutkowska, & Rachon, 2015; Metz, 2016).

Phthalates are alkyl diesters of phthalic acid and are used as plasticizers in PVC products, as solvents and fixatives in personal care products, children's toys and as additives in the enteric coating of some drug tablets. Since these compounds are not covalently bound to the products, they easily leach from them, leading to high human exposure (Figure 3) (Ji et al., 2014). Phthalate exposure has been estimated by biomonitoring studies, and ranges between 1 and 2 µg/kg bw/d of a single compound for adults and up to 4 µg/kg bw/d for children (Bergh, Torgrip, Emenius, & Ostman, 2011; Fromme et al., 2004). Oral consumption of contaminated food and dermal absorption from personal care products are considered the main exposure routes (Diamanti-Kandarakis et al., 2009). Of particular interest is the presence of phthalates in the atmospheric aerosol, forming part of the organic content of particulate matter (PM<sub>2.5</sub>). Phthalate concentrations can range from 1 to 100 ng/m<sup>3</sup>

outdoors and up to 1,000 ng/m<sup>3</sup> indoors with DEHP and DBP being the main compounds detected (Frederiksen, Skakkebaek, & Andersson, 2007; Swan, 2008).

In subsequent paragraphs, we will delve into the effect of bisphenols and phthalates on the actions of the immune system.

## 6 | PERINATAL BPA ADMINISTRATION EFFECTS ON THE IMMUNE SYSTEM

Different BPA effects have been reported on the immune system; however, they vary depending on whether they were performed *in vivo* or *in vitro*, or if they are epidemiological studies in humans. *In vivo*, the effects reported may seem contradictory, but they are not, because the reported effects depend on the animal species used, the dose, the administration route, the sex of the animal, the age, and the animal's developmental stage during which BPA was administered. Furthermore, many reports do not consider that the immune response must be studied by challenging the immune components, so there is little information about BPA effects on the immune response during disease.

## 7 | BPA AS IMMUNOMODULATOR

Macrophages and dendritic cells (DCs) are the main phagocytic cells that play an important role in the maintenance of organism homeostasis (Gordon & Martinez-Pomares, 2017). Furthermore, they express the two ER isoforms (ER $\alpha$  and ER $\beta$ ) through which BPA could exert its effects (Harkonen & Vaananen, 2006; Segovia-Mendoza & Morales-Montor, 2019). Yamashita et al. described that BPA stimulated pro-inflammatory cytokine production including interleukin (IL)-1, IL-6 and IL-12, and increased the expression of the costimulatory molecule CD86 expression in murine peritoneal macrophages (Yamashita, Sugiura, Yoshida, & Kuroda, 2003). In concordance with this study, mouse peritoneal macrophages under M1 type conditions that were exposed to low concentrations of BPA promoted polarization toward the M1 subtype by the upregulation of IRF5 expression, as well as tumor necrosis factor (TNF- $\alpha$ ), IL-6, and monocyte chemoattractant protein-1, while the same BPA exposure to macrophages under M2 type conditions inhibited the M2 subtype polarization by the down-regulation of IL-10 and transforming growth factor-beta (TGF- $\beta$ ) (Lu et al., 2019). In addition, a BPA analog, (BPA-glycidyl-methacrylate), was able to induce stimulation of TNF $\alpha$  production with a concomitant increase of

the expression of surface molecules (CD11, CD14, CD40, CD45, CD54, and CD80), on the RAW264.7 murine macrophage cell line (Kuan, Li, Huang, & Chang, 2012). Interestingly, BPA can induce alternative macrophage activation (M2), reducing the production of different cytokines, IL-6, IL-10, and IL-1 $\beta$ , in macrophages derived from human peripheral blood monocytes (PBMCs) stimulated or not with lipopolysaccharide or IL-4. It was also reported that BPA treatment increased IL-10 and decreased IL-6 production in macrophages classically activated (M1) (Li et al., 2018). Of note, the immune-modulatory effects of BPA also been reported to occur in macrophages derived from the carp (*Cyprinus carpio*) fish, where its exposure generated immunotoxicity mediated by the increase of long noncoding RNAs expression that affected different signaling pathways related to the immune response such as NF- $\kappa$  B, Toll-like receptor, B-cell receptor, and the Jak-STAT signaling pathway (Liu et al., 2020).

On the other hand, DCs are antigen-presenting cells par excellence; they play a fundamental role at the beginning of the immune response and in polarization and regulation. Limited studies have investigated the effects of BPA on DCs. Delving into this aspect, studies of DCs derived from human PBMCs that have been exposed to the treatment of BPA have shown that it promoted polarization into a Th2 immune response, this effect was mediated by the enhancement of the chemokine ligand 1 (CCL1) expression, the IL-5, IL-10, and IL-13 production as well as the expression of the transcription factor GATA3 in the presence of TNF $\alpha$  (Guo et al., 2010). In addition, the exposure of BPA or its different analogs also affects the endocytic capacity, the costimulatory molecule expression, activation markers such as HLA-DR as well as CD1a expression (an important protein mediating antigenic presentation) of human DCs (Svajger, Dolenc, & Jeras, 2016). The above indicates that not only the BPA but also the industrial alternatives to replace it have an important impact on the function of the immune system.

Mast cells are resident tissue cells that play a key role in inflammatory and allergic processes. These cells are characterized by their high content of cytoplasmic granules containing preformed mediators that include the vasoactive amine histamine, proteases, as well as some cytokines. Mast cells may be activated by a variety of stimuli through the numerous receptors on their surface. Upon activation, mast cells can release preformed as well as a several distinct newly synthesized mediators (Gilfillan, Austin, & Metcalfe, 2011; Gilfillan & Beaven, 2011). In a two-generational study, O'Brien reported that perinatal BPA exposure through maternal diet caused an increase in mast cell-derived leukotrienes, histamine, prostaglandin E2, TNF $\alpha$ , and IL-13 molecules in the

offspring, suggesting a greater activation of these cells that promote the allergic reaction (O'Brien, Dolinoy, & Mancuso, 2014). However, there are not many studies about it; thus, further studies will be needed to evaluate the role of BPA exposure on mast cell response and its association with allergic diseases.

T lymphocytes (TL) are cells of the adaptive immune system, they can be divided into cytotoxic TLs (CTLs) or T helper lymphocytes (ThL), which can differentiate into Th1, Th2, Th9, Th17, and Th33, based on their cytokine secreting pattern. These cells express different hormone receptors, thus sex steroids can regulate TLs differentiation and their response (Segovia-Mendoza & Morales-Montor, 2019). Some studies have reported that BPA exerts its effects throughout the binding to hormone receptors with a consequent modulation of ThL response and polarization (Th1, Th2, and Th17). In addition, the effect of prenatal exposure of BPA on the specific immune response against the OVA antigen was to decrease the percentage of the TCD4+ cells and the IFN- $\gamma$  secretion (Kuo, Yang, Kuo, & Hung, 2012; Menard et al., 2014; Yoshino et al., 2004). It is important to mention that the perinatal exposure of BPA at Day 9.5 of gestation until weaning produced changes in cytokine expression, including G-CSF, GM-CSF, IL-12p70, IL-1 $\alpha$ , IL-1 $\beta$ , TNF $\alpha$ , and RANTES in serum levels (Holladay et al., 2010). Likewise, BPA administrated to mice in their drinking water during the perinatal period, increased the percentage of Th17 cells and levels of ROR $\gamma$ t protein in conjunction with a significant decrease of Treg cells and Foxp3 protein. Additionally, this compound also modulated the expression of different cytokines IL-17, IL-21, IL-6, and IL-23 in a dose-dependent manner (Dong et al., 2020; Yan, Takamoto, & Sugane, 2008). Moreover, some studies have reported that BPA was able to generate T cell polarization, directing it to a Th2 response (Nowak, Jablonska, & Ratajczak-Wrona, 2019; Yan et al., 2008; Yoshino et al., 2003).

B lymphocytes are cells whose importance lies in humoral immunity, since they are able to differentiate into plasma cells (PCs), which are responsible for the production of antibodies such as IgA, IgG, IgE, IgD, and IgM (Tsai, Hung, Chang, & Lin, 2019). In different studies, it has been observed that perinatal exposure of BPA may modify in a different way the production of antibodies by these cells derived from animal models where different antigenic stimuli have been used (Del Rio-Araiza et al., 2020; Hernandez Avila, Palacios-Arreola, Nava-Castro, Morales-Montor, & Ostoa-Saloma, 2019; Yoshino et al., 2003). Therefore, it was reported that gestational exposure to BPA generated increased production of IgG1 and IgG2a antibodies, with predominance of IgG2a antibodies in male offspring (Yoshino et al., 2004). Some

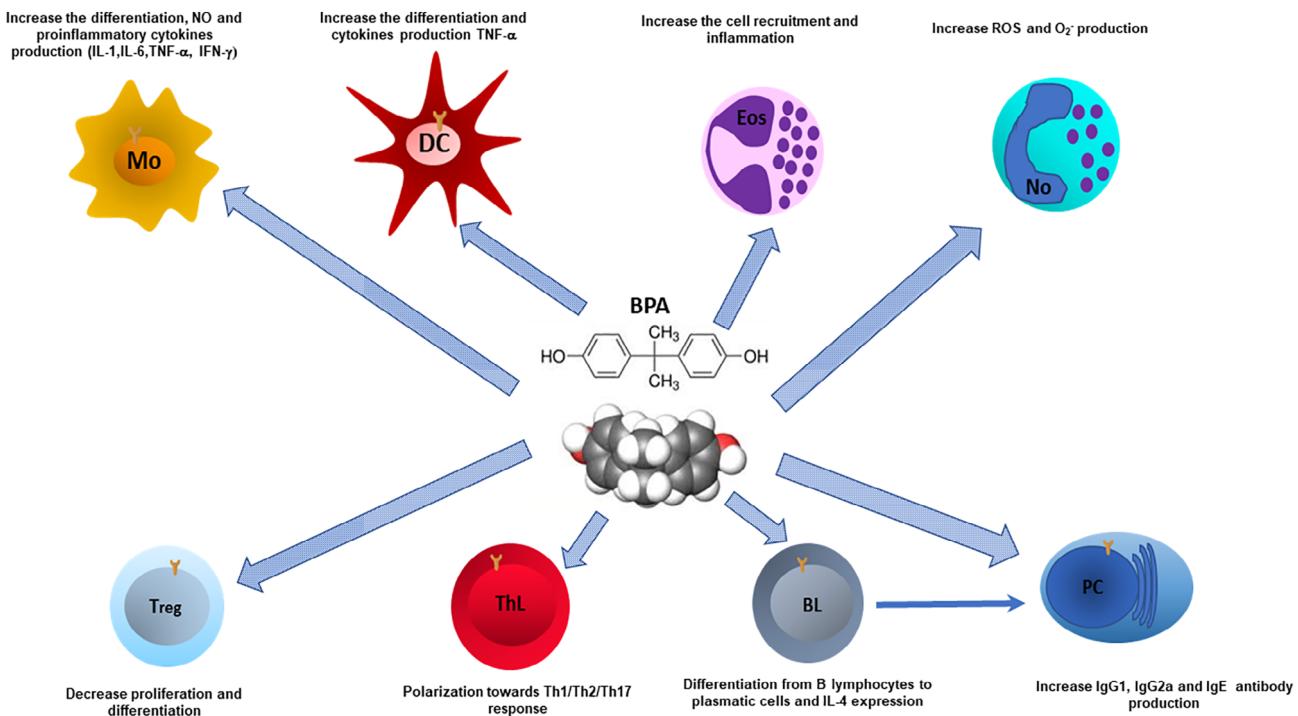
reports have mentioned that perinatal exposure of BPA in animal models also resulted in high titers of anti-OVA IgG or IgE antibodies in the offspring, the increase of the last type of immunoglobulin (Ig) has been linked with the modulation of the function of mast cells and with the development of asthma (Menard et al., 2014; Midorohoriuti, Tiwari, Watson, & Goldblum, 2010). A chart that summarizes all known effects of BPA on human immune system cells (SCs) are depicted in Figure 4.

## 8 | PHTHALATES AS IMMUNOMODULATORS

Perinatal exposure of phthalates has also been associated with high Ig levels. For instance, in mouse models, the perinatal administration of BBP evoked an elevation in serum IgG1 and IgG2a level in the offspring with a simultaneous increase of IFN- $\gamma$  and IL-17 production (Elter, Wagner, Buchenauer, Bauer, & Polte, 2020). In addition, in an ovalbumin (OVA) sensitization weanling mouse model, the exposure to DEHP modified the IL-21 and IL-4 expression by the follicular T helper cells (Thf) and induced augmentation of the OVA-specific IgE and IgG1 production, an effect that was related to the differentiation of B cells into PCs (Han et al., 2014; He et al., 2013). Interestingly, the

exposure to this compound during different stages in childhood increased the risk of allergic sensitization and atopic disorders mediated by the modulation of IgE (Beko et al., 2015; Wang, Lin, Lin, Hsieh, & Chen, 2014). The above has allowed establishing a positive correlation between the exposure of these compounds and the prevalence of diverse pathologies in children that are characterized by hypersensitivity such as asthma, atopic dermatitis, rheumatoid arthritis, among others (Robinson & Miller, 2015).

In animal asthma models, the most studied phthalate DEHP has been shown to increase pulmonary inflammation, antibody production (specially IgE), IL-4 and IFN- $\gamma$  production (Guo et al., 2012). This Th2 polarization has also been observed in an allergic rhinitis model, where DEHP exposure leads to higher IL-13 levels in the nasal epithelium (He et al., 2013). In cutaneous hypersensitivity models, different EDCs including phthalates have also been shown to promote a Th2 response, as denoted by a high IL-4 and IFN- $\gamma$  production (Kato et al., 2006). Moreover, the prenatal exposure of phthalates in different murine allergic models has been related to the modulation of different chemoattractant molecules of DCs, such as thymic stromal lymphopoitietin (TSLP), CCL17, and CCL22 (Koike et al., 2010; Larson et al., 2010; Matsuo et al., 2019; Shigeno, Katakuse, Fujita, Mukoyama, &



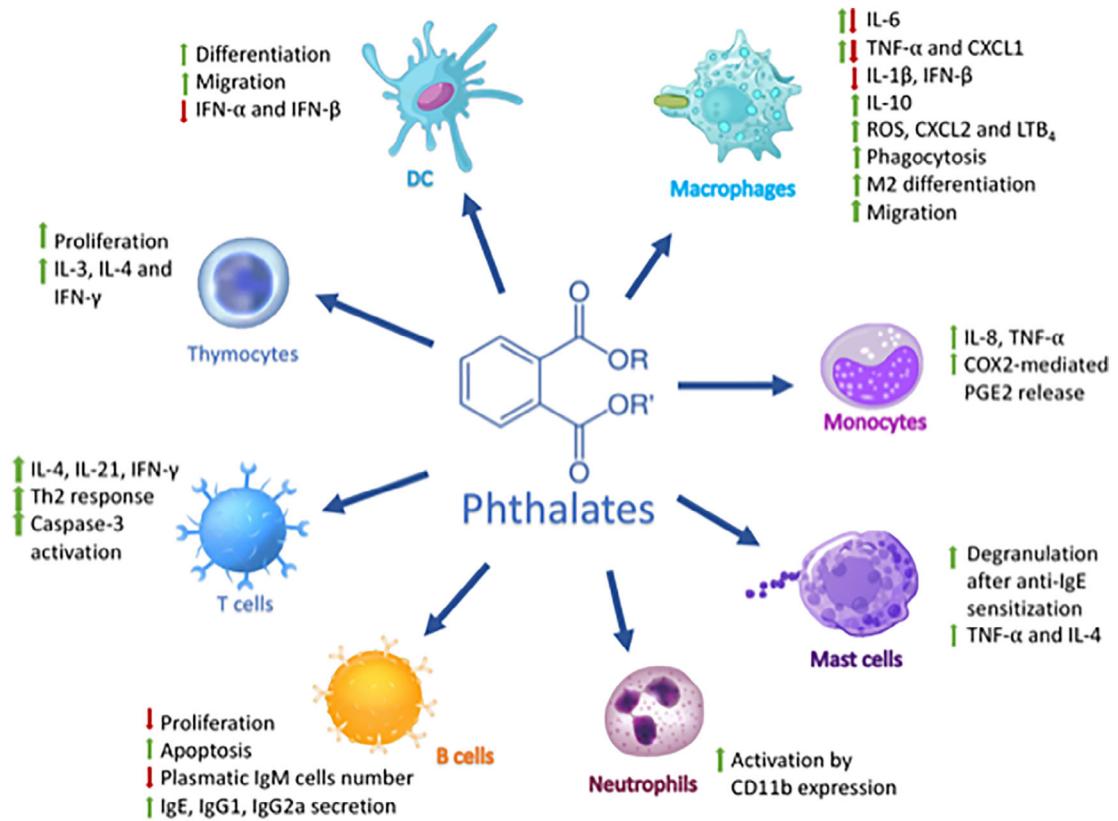
**FIGURE 4** Effects of BPA on the cells of the immune system. The bisphenol A (BPA) effects in different immune cells are variable depending on the type of model, in vivo or in vitro, the animal species used, the dose, the administration route, and the stage of development in which it is administered. However, all studies have a common conclusion that BPA affects the following immune cells: BL, B lymphocytes; DC, dendritic cells; Eos, eosinophils; Mo, macrophages; No, neutrophils; PC, plasmatic cells; ThL, T helper lymphocytes; Treg, T regulatory lymphocytes

Watanabe, 2009), which coincides with common events such as activation of mast cells and the high recruitment of antigen-presenting cells like DCs and macrophages. In addition, it has been observed that exposure to some phthalates, particularly DEHP, impacted the Th1/Th2 balance with an increased infiltration of macrophages together with a higher expression of pro-inflammatory cytokines such as IL-1 $\beta$  and IFN- $\gamma$  (Okdah, 2013; Pei, Duan, Ma, Zhang, & Guo, 2014; Yamashita et al., 2003). A chart that summarizes all known effects of BPA in the human immune SCs are depicted in Figure 5.

## 9 | IMMUNOMODULATORY EFFECTS OF PHTHALATES IN HUMANS

Epidemiological studies, albeit with varying results, support the immunomodulatory effects of phthalates, particularly

due to prenatal exposure. A 70% higher risk of asthma diagnosis at age 5–11 has been observed in children born to women with higher urinary levels of BBP and DBP metabolites during their pregnancies (Beko et al., 2015; Bornehag & Nanberg, 2010; Johnk et al., 2020; Robinson & Miller, 2015). In addition, the association between asthma prevalence in children and maternal urinary levels of different phthalates and their metabolites has been observed in different countries (Bertelsen et al., 2013; Ku et al., 2015; Shi et al., 2018). At the molecular level, there exists a controversy in the effect of the different phthalates and the modulation of IgE and IL-33, that might be associated with allergic pathologies (Ashley-Martin et al., 2015). However, a positive association between maternal urinary levels of different phthalates (MEP, mono-(2-ethylhexyl) phthalate [MEHP], MBP, and monobenzyl phthalate [MBzP]) or their metabolites and IgE levels in children at ages 2 and 5 have been found, especially in allergic diseases (Wang et al., 2014). Interestingly, this association was mainly associated with significant effects in



**FIGURE 5** Immunomodulatory effect of phthalates. In general terms, phthalate exposure leads to higher immunoglobulin levels. For one of the most studied phthalates diethylhexyl phthalate (DEHP), the increase in IgE seems to be mediated by the promotion of differentiation of B cells into plasma cells and by the stimulation of follicular T helper cells (Thf), producing higher IL-21 and IL-4. Phthalate exposure has been shown to increase Th2 (dibutyl phthalate [DBP], DPP, DEHP, and DINP) and Th17 cytokines (DBP). DEHP exposure leads to higher IL-13 levels. DBP, DPP, and DINP have been shown to promote Th2 response, as denoted by a high IL-4 production. Moreover, phthalate exposure also stimulates the production of chemoattractant molecules, such as TSLP, chemokine ligand 17 (CCL17), and CCL22. DEHP, causing an increased infiltration of macrophages and other leukocytes in the testis, together with a higher expression of pro-inflammatory cytokines, such as IL-1 $\beta$  and IFN- $\gamma$ .

boys. Regarding current exposure in adults, the NHANES 2005-2006 study found an association between urinary levels of high-molecular-weight phthalate metabolites and allergic sensitization (Hoppin et al., 2013). Furthermore, the urinary concentration of the metabolite of MBzP correlated with the presence of allergic symptoms. However, this same study found that in children there was an inverse relationship between urinary concentrations of phthalate metabolites and the incidence of asthma and high fever (Hoppin et al., 2013). Another study performed in adults allergic to dust mite, the inhalation of DEHP-containing dust modified the expression of G-CSF, IL-5, and IL-6 in a differential fashion, depending on the concentration. At low levels, those cytokines increased, while at high concentrations both G-CSF and IL-6 decreased (Deutschle et al., 2008; Potera, 2008). It is interesting to note that, similar to what is observed with some hormones, the dose-response relationship seems to be nonmonotonic. Unlike, the effect of the murine perinatal exposure of phthalates in terms of activation of DCs through the elevation of levels of chemoattractant molecules such as the TSLP, epidemiological studies did not find a real association (Ashley-Martin et al., 2015). In relation to the above, the neutrophil's chemotaxis has also been inhibited by the exposure of MEHP and DEHP in both neonatal and adult cells, presenting a more outstanding effect in neonatal cells. Interestingly, this effect was mediated by the binding of phthalates to PPAR $\gamma$  receptor, contributing to its inhibition and with the decrease of the anti-inflammatory signaling (Vetrano et al., 2010). All of these cellular effects remind us that EDCs act by multiple pathways and in multiple cells and tissues.

Furthermore, both bisphenols and phthalates exert sexually dimorphic effects, affecting male and female individuals differently. The information above point to both EDCs being strong immunomodulators that affect offspring exposed in utero to them. In summary, perinatal or neonatal exposure to these compounds either in animal models or in humans is related to the fact that both have been related to a wide range of pathologies (Strakovsky & Schantz, 2018) (Figure 5).

Importantly, both kinds of compounds can also induce epigenetic changes when administered at critical developmental periods; thus, now we will next delve into their effects on the predisposition of developing certain types of cancer.

## 10 | BREAST CANCER AND PERINATAL OR NEONATAL EXPOSURE OF BISPHENOL AND PHTHALATES

Breast tissue is known to be highly sensitive to the effects of steroid hormones such as estrogens. In fact, different

biological processes such as ductal growth, elongation, branching, differentiation of mammary gland cells and several genes including those that govern cell proliferation are transcriptionally regulated by this hormone (Tian, Ran, Zhang, Yan, & Li, 2018). Likewise, synthetic estrogens such as diethylbestrol have been shown to increase the mammary epithelial cell number, an effect that has been related to the development of mammary neoplasm (Kawaguchi et al., 2009; Palmer et al., 2006). In line with that, perinatal exposure to BPA has also been associated with the promotion of mammary carcinogenesis in mouse and rat models through the activation of proliferating and pro-tumoral pathways, WNT-4 and receptor activator of nuclear factor  $\kappa$ B ligand. Moreover, the amount of ER alpha (ER $\alpha$ ) positive cells, as well as different steroid receptor coactivators and growth factor receptors with mitogenic downstream pathways were significantly upregulated (Ayyanan et al., 2011; Jenkins et al., 2009; Lamartiniere, Jenkins, Betancourt, Wang, & Russo, 2011; Murray, Maffini, Ucci, Sonnenschein, & Soto, 2007). Additionally, the exposure of different analogs of BPA such as BPS and BPF in pregnant mice also produced accelerated mammary gland development in the resulting female offspring at different postnatal days up 14 months. In fact, alterations in mammary gland morphology persisted into late adulthood influencing the susceptibility to spontaneous preneoplastic epithelial lesions and inflammation (Tucker, Hayes Bouknight, Brar, Kissling, & Fenton, 2018). All of these changes might be partially mediated by epigenome changes at the mammary gland level as well as alteration in gene expression patterns. Supporting this fact, the prenatal exposure of BPA in rats was shown to promote outstanding histone trimethylation (Dhimolea et al., 2014; Doherty, Bromer, Zhou, Aldad, & Taylor, 2010). These genetic events were observed in the postnatal and adult mammary gland of the offspring born to rats exposed to BPA, contributing to the development of preneoplastic and neoplastic lesions that manifest during adulthood (Dhimolea et al., 2014). As we mentioned before, perinatal exposure of BPA can increase the risk of breast cancer; however, the molecular mechanisms involved in this process remain a mystery. In order to understand the mechanisms involved in this modulation, another group performed experiments using mice and evaluating the in utero exposure of this compound (Potischman & Troisi, 1999). BPA modulated the protein expression of classical targets of the ER pathway such as cyclin D1, c-myc, and Bcl-2; moreover, the concurrent activation of erbB2, EGFR, erbB-3, Erk1/2, and Akt, and the upregulation of their respective growth factors/ligands was also reported (Ma et al., 2020). It is known that the proliferation of breast tissue is governed by both the ERs and their natural ligands and that females have higher levels of them compared to males. Therefore, sex specific

effects would be expected. In line with this prediction, male offspring born to pregnant rats that received low concentrations of BPA also showed increased mammary outgrowth, while the female offspring developed intraductal hyperplasia, supporting previous work (Mandrup, Boberg, Isling, Christiansen, & Hass, 2016). It was concluded that low-dose exposure to BPA can affect mammary gland development in male and female rats, which could be extrapolated to humans because critical murine periods of development and human mammary gland development are known to be analogous (Osborne, Rudel, & Schwarzman, 2015).

Most of the pro-tumoral effects of perinatal or neonatal BPA exposure related to the development of breast cancer has been directly associated with the regulation of genes or proteins activated by the ER. However, it has also been observed that a single neonatal exposure in mice predisposes to developing larger mammary tumors, effects associated with the modulation of both immune cells and molecules infiltrated in the tumor microenvironment when the mice reach adulthood (Palacios-Arreola, Nava-Castro, Rio-Araiza, Perez-Sanchez, & Morales-Montor, 2017). The above indicates that the effects of perinatal administration of this compound affect not only cells in breast tissue but also immune cells, which also have steroid receptors (Segovia-Mendoza & Morales-Montor, 2019). This also suggests that BPA exposure promoted an epigenetic reprogramming with long-lasting effects in other cell types. Of note, it is important to highlight that perinatal exposure of this compound not only causes the development of mammary neoplasia but also predisposes offspring to cancer carcinogenesis when they are exposed just once to a potent carcinogen such as 7,12-dimethylbenz(a)anthracene (Betancourt, Eltoum, Desmond, Russo, & Lamartiniere, 2010).

Regarding exposure to phthalates during critical periods of development, it can be established that, like bisphenols, they promote sexual dysfunction in male and female individuals as well as breast cancer progression (Grande, Andrade, Talsness, Grote, & Chahoud, 2006; Gray et al., 2000; Meeker et al., 2009; Moyer & Hixon, 2012; Terry et al., 2019). However, there are still few studies about the perinatal exposure of these compounds and their effects related to breast cancer promotion in offspring. In order to delve into this aspect, experiments of the exposure to BBP in an *in utero* rat model have been shown to induce modifications in the architecture and proliferative index of the mammary gland as well as increasing the susceptibility to carcinogenesis (Moral et al., 2011). Moreover, these chemical agents can also favor the proliferation of breast cancer cells (Fernandez & Russo, 2010), indicating that their exposures not only have a pro-tumoral effect during

critical periods but also at the beginning of the disease. In fact, their presence has been identified in women with breast cancer, and exposures to them have also been related to chemoresistance to therapy for this pathology (Holmes et al., 2014; Hsu et al., 2015; Lopez-Carrillo et al., 2010). All of these pro-tumoral effects of phthalates have been related to interactions with the ER rather than to epigenetic changes, in the case of DEHP perinatal exposure, which was not associated with epigenetic changes in breast cancer-related genes (Cheng et al., 2018). It has not been investigated whether phthalates also affect the specific immune tumor microenvironment, thus increasing the risk of more aggressive tumors.

## 11 | COLON CANCER AND PERINATAL OR NEONATAL EXPOSURE OF BISPHENOLS AND PHTHALATES

Starting from the notion that bisphenols and phthalates can bind and regulate several estrogen-dependent genes, the current studies that have correlated colon cancer development with estrogen pathways, and the possible relationship between perinatal and neonatal exposure to these compounds and the development of this pathology will be discussed in the following paragraphs.

It has been reported that perinatal exposure to BPA caused an alteration of colon cell permeability and local inflammation. The above was mediated by the elevation of levels of interferon- $\gamma$ , IL-17, and IgA (Malaise et al., 2018). Similar effects in terms of colon cell permeability and inflammation were observed in the offspring of rats that received this compound. These effects seemed to be dimorphic, being highly manifested in female rather than in male offspring (Braniste et al., 2010). They were linked with BPA binding to ER $\beta$ . It is known that in rodents and humans this receptor is predominantly found in the colon (Campbell-Thompson, Lynch, & Bhardwaj, 2001). Supporting this fact, the exposure of BPA in ER $\beta$  overexpressing colon cancer cells has been associated with elevated colon cancer growth. BPA seems to block the estrogen actions mediated by this receptor, for instance BPA impaired the E2-induced activation of the apoptotic cascade which is considered to be the main route of protection of endogenous estrogen hormone against colon cancer growth (Bolli, Bulzomi, Galluzzo, Accocia, & Marino, 2010). In addition, phthalate exposure increased the multidrug resistance gene in colon cancer promoting drug chemoresistance (Takeshita, Inagaki, Igarashi-Migitaka, Ozawa, & Koibuchi, 2006). It is important to mention that perinatal exposure of bisphenols and phthalates modify the colon microbiota;

whose activation has been recently linked with colon cancer development (Hu et al., 2016; Lai, Chung, Li, Wan, & Wong, 2016).

Thus, it can be assumed that perinatal exposure to BPA or phthalates alters the microbiota and immune functions leading to a pro-tumoral inflammatory micro-environment in the colon of adult offspring that favors the development of colon cancer. However, direct effects of these compounds are not fully addressed in this type of cancer.

## 12 | PROSTATE CANCER AND PERINATAL OR NEONATAL EXPOSURE OF BISPHENOLS AND PHTHALATES

Similar to breast cancer pathophysiology, prostate cancer also depends on steroid receptor activity including that of the androgen receptor. However, several studies have pointed out that estrogen can predispose to prostate cancer development through the induction of epithelial to mesenchymal transitions induced by the activation of the different nuclear and membrane ERs (Dobbs et al., 2019). The effects of BPA exposure in critical periods of development mimic the procarcinogenic effects on prostate cells induced by estradiol or estradiol benzoate, since the exposure of both compounds in early life periods also alter the morphology of prostate cells and impaired gene expression in conjunction with the epigenetic methylation profile (Prins, 2008; Saffarini, McDonnell-Clark, Amin, Huse, & Boekelheide, 2015). In addition to the above, BPA can also bind to the androgen receptor, interfering with its molecular activities (Teng et al., 2013). With respect to the mechanism of BPA in prostate carcinogenesis, it has been reported that neonatal exposure to this compound in low or high doses has shown to increase the prostate neoplastic lesions along with alteration in the prostate epigenome, thus predisposing to prostate carcinogenesis. One of the mechanisms involved in the promotion of prostate cancer is the silencing of different metabolic enzymes, such as phosphodiesterase Type 4 (Ho, Tang, de Belmonte Frausto, & Prins, 2006; Prins, Tang, Belmonte, & Ho, 2008), whose aberrant expression has been associated with the development of certain types of cancer in a cAMP-dependent manner (Henderson et al., 2014). Moreover, neonatal exposure to BPA also induces changes in enzymes with a crucial role in chromatin remodeling such as DNA methyltransferases (Dnmt1, Dnmt3a, and Dnmt3b); the authors further reported that neonatal exposure to this compound induced transitory or permanent epigenetic

marks that were detected in early and adult life. This is the case of the hypomethylation of the promoter of nucleosome binding protein-1, an important molecule involved in cell differentiation (Shirakawa et al., 2009; Tang et al., 2012). In addition, another study supported this finding. BPA exposure of newborn rats resulted in the modulation of the methylation of promoter regions of genes related to embryonic SC pluripotency, cell-to-cell signaling and interaction, cell-mediated immune response, cellular growth and proliferation, nucleic acid metabolism, molecular transport, cellular assembly, and organization (Cheong et al., 2016). The epigenetic changes induced by BPA exposure have been corroborated not only in animal models but in vitro experiments, where this EDC also modified the epigenetic signature of transcripts encoding nuclear hormone receptors as well as histone and DNA methylation in prostate epithelial cells (Renaud et al., 2019). In addition, this compound can also induce centrosomal abnormalities, microtubule nucleation, and anchorage-independent growth in prostate cancer cell lines (Tarapore et al., 2014). Other studies have reported that BPA administration in pregnant mice caused an increased proliferation rate of basal epithelial cells located in the primary ducts of the prostate as well as an increased number of androgen receptors. The effect on proliferation was mediated by the activation of proliferating cell nuclear antigen (PCNA) and mouse keratin 5 (Timms et al., 2005). Despite all the pro-tumor effects of BPA in relation to prostate cancer, its urinary levels have not been identified as a diagnostic or prognostic indicator in this pathology.

Phthalates similar to bisphenols can promote prostate cancer. They can interfere with several androgenic actions that have been linked to impaired reproductive disorders in males as well as alterations in Sertoli cell function (Gray et al., 2000; Jurewicz & Hanke, 2011; Knez, 2013; Paumgartten, 2015). Supporting this fact, the perinatal exposure to DEHP has been linked to alteration in prostate weight and with reduction of the expression of several androgen-regulated genes in the prostate (Christiansen et al., 2010). Although there are still many gaps in the knowledge of the effects of these compounds in this type of cancer, it has been reported that perinatal exposure to phthalates evokes transgenerational effects in the offspring at many levels, including pro-tumoral effects in the prostate. In fact, nowadays the urinary levels of several phthalates such as DEHP, DBP, and BBP and the incidence in this pathology have been identified in humans and considered as prognostic indicators of the development of this type of cancer. However, their biological mechanisms of their action have not yet been fully elucidated (Chuang et al., 2020).

## 13 | OVARIAN AND ENDOMETRIAL CANCER AND PERINATAL OR NEONATAL EXPOSURE OF BISPHENOLS AND PHTHALATES

There is strong evidence supporting the fact that bisphenols and phthalates are reproductive toxicants, in deed, these EDC, are capable of interfering with reproductive systems, although varies depending on the structure of the parental chemical or their metabolites (Kay, Chambers, & Foster, 2013; Meeker et al., 2009). In mammals, the development and function of the female tract depends on the hormone concentration and balance; variation caused by EDCs may result in many abnormalities, including menstrual cycle irregularities, impaired fertility, endometriosis, polycystic ovarian syndrome (PCOS), spontaneous abortion, and alteration of female hormone concentration (Crews & McLachlan, 2006).

In humans, epidemiological studies suggest a correlation between phthalate concentrations in cord blood and lower gestational age at delivery (Zhang et al., 2009). On the other hand, neonatal exposure of BPA is capable to interfere with (a) hypothalamic–pituitary–ovarian axis, affecting brain sexual differentiation, (b) altering ovarian morphology, (c) expression of gonadotropin releasing hormone (GnRH), (d) inducing cystic endometrial hyperplasia, (e) reducing the pool of primordial follicles in the ovary, and (f) directly increasing ovarian androgen synthesis (Giulivo, de Lopez Alda, Capri, & Barcelo, 2016). Furthermore, BPA affects oocytes, including decreased ovarian weigh, increased incidence in multiple oocyte follicles, and disturbances in prophase events (Rivera, Varayoud, Rodriguez, Munoz-de-Toro, & Luque, 2011). In addition, BPA and phthalates may enhance the development and promotion of endometriosis and PCOS, through the activation of the hypothalamic GnRH pulse generator leading to a constant increase of plasma luteinizing hormone concentration which in turn stimulate the ovarian androgen production and impair proper ovarian follicle development (Vabre et al., 2017).

It is challenging to evaluate directly the perinatal or neonatal effects of EDC in humans. First, the fetus is very sensitive to EDCs because of its dependency on hormones for development (Diamanti-Kandarakis et al., 2009), in addition, catabolic enzymes for EDCs are only produced after birth and fetal circulation is slower than maternal, leaving the fetus to longer exposure of EDCs (Doerge, Twaddle, Vanlandingham, Brown, & Fisher, 2011); neonatal babies after BPA exposure present lower capacity to metabolize BPA due to low expression of the liver enzyme, uridine 5'-diphospho-glucuronosyltransfer. Second, although bisphenols, phthalates, and their metabolites

are found in urine, serum, breast milk, and semen, most human biomonitoring studies are in urine and serum with variable results depending on the acquisition time: BPA has been detected in early gestation of human pregnancy in serum at ng/ml levels and at significantly higher levels (up to fivefold and greater) in amniotic fluid suggesting accumulation early in fetuses (Wang, Zhu, & Kannan, 2019); BPA and phthalates levels strongly depend on dietary habits and it is important to consider that the reported half-life of phthalates diesters in blood plasma or urine of humans and rodents was less than 24 hr (Arbuckle et al., 2014; Quiros-Alcalá et al., 2013; Yang et al., 2018). Finally, EDCs effect is observed in the F3 generation with no direct exposure to EDC; this trans-generational effect is presumably due to epigenetic alterations of the germ line, such as DNA methylation, histone modification, or noncoding RNAs (Brehm & Flaws, 2019).

Some evidence between BPA levels and incidence of ovarian or endometrial cancers in humans are (a) BPA exposure could mimic the effects of estrogen in ovarian cells (Dekant & Volk, 2008; Upson et al., 2014); (b) human ovarian epithelial cancer cells express higher levels of ER than cells from benign tumors and normal ovary (Akahira et al., 2002); and (c) chronic BPA exposure induces augment in cystic ovaries and cystic endometrial hyperplasias with potential to turn into neoplastic lesions (Newbold, Jefferson, & Padilla-Banks, 2007). The mechanisms involved in EDCs carcinogenesis are: in ovarian cancer cell line (OVAR-3) low concentration of BPA can induce proliferation through the cooperation with leptin receptor protein to inhibit caspase-3 expression and activity (Ptak & Gregoraszczuk, 2012); EDCs can upregulate mRNAs involved in cell cycle such as, cyclin D1, CDK4, cyclin A, PCNA, E2F1, and E2F3 promoting cell proliferation in ovarian tumorigenesis; opposite, EDCs can downregulate mRNA including p21, Weel-1, and GADD45, which inhibit cell proliferation and also downregulate CDK-4 inhibitors, responsible of G1 arrest through binding cyclin-CDK complexes (Hoffmann, Fiedor, & Ptak, 2017); BPA play an important role in migration activating protein kinase and phosphatidylinositol 3-kinase pathways (Ptak, Hoffmann, Gruca, & Barc, 2014). BPA can also induce mutations in the BRCA1 and two genes in the ovarian cells (Kundakovic & Champagne, 2011).

Alternatively, BPA is able to inhibit the expression of pro-apoptotic genes like FAS, FADD, RAIDD, caspases, CAD, and BOK; also, EDCs can induce the expression of pro-survival genes like Bcl-xL and Mcl-1 or promote growth of ovarian cancer cells via ER-CXCL12-CXCR4 signaling axis. One of the major causes of mortality driven by ovarian cancer cells are metastasis driven by

switching E-cadherin into N-cadherin, which diminish cell adhesion, and also stimulate overexpression of matrix metalloproteinases (MMPs), such as MMP-2 and -9 that degrade extracellular matrix and basement membranes promoting tumor invasion. BPA stimulate granulosalutein cells to express MMP-9 and -2, which provide a poorer outcome for the patient due to a more aggressive phenotype of the tumor (Shafei et al., 2018).

It is clear that pregnant women have higher urinary EDCs levels than nonpregnant women, suggesting that there is higher exposure to the fetus. Despite the fact that maternal blood concentrations of ~2.5 ng/ml versus umbilical cord blood concentrations of ~0.5 ng/ml suggest placental protection, after BPA exposure elevated risk of lower birth weight, smaller size for gestational age, higher fetal leptin, and lower adiponectin is observed in newborns. Therefore, early-life exposure to even low doses of EDCs may have a greater impact on adult disease outcomes.

## 14 | CERVICAL CANCER AND EARLY EXPOSURE OF BISPHENOLS AND PHTHALATES

BPA is associated with increased risk of cervical, ovarian, and uterine cancers; although cervical cancer is not estrogen dependent neoplasm, nanomolar concentration of BPA can promote migration and invasion in cervical cancer HeLa, SiHa, and C-33A cells, dysregulating estrogen signaling pathway<sup>24</sup>. Moreover, BPA levels in urine were increased in cervical cancer woman<sup>25</sup>. Similarly to human ovarian cancer cells, there is an upregulation of MMP-9 of cervical cancer cells, but activated by NF-κB, which in turn trigger migration and invasion of cells, when translocated to the nucleus (Ma et al., 2015).

## 15 | LUNG CANCER AND EARLY EXPOSURE OF BISPHENOLS AND PHTHALATES

Exposure of air pollution and dietary habits during embryonic and early-life development can result in placental epigenetic modifications and fetus reprogramming, which can influence disease susceptibility in later life. Particular attention has focused on the exposure of air pollution on early life development and child's health during pregnancy; originally, only low birth weight, preterm delivery, and neural development was reported. Among the most relevant chemical compound associated with air pollution, we find EDCs such as bisphenols and

phtalates, which are involved in lung carcinogenesis beside cigarette smoke.

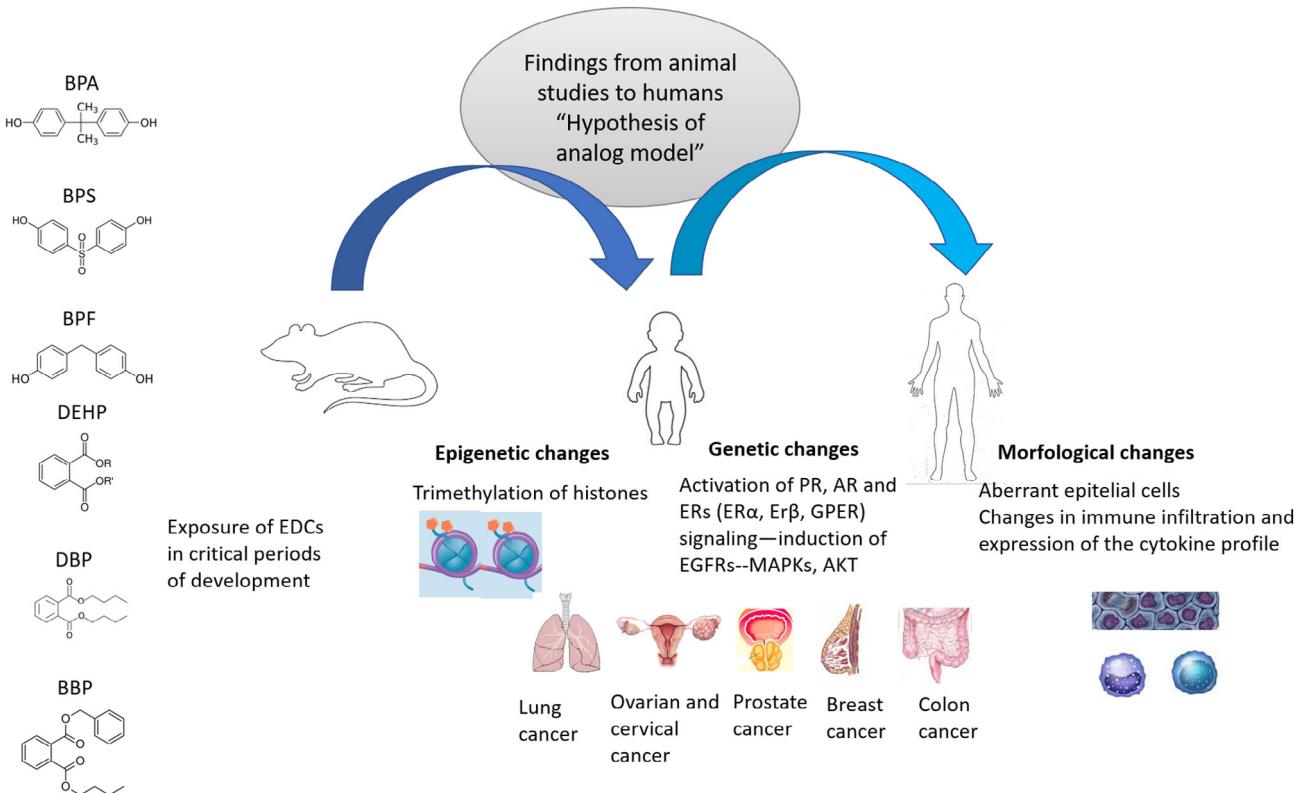
These EDCs have higher levels detected in urine, for instance, maternal exposure to BPA in the workplace was associated with decreased birth weight (Miao et al., 2011), indicating the sensitivity of the fetus. Compared with other embryonic tissues, placenta is in more direct contact with air pollution and is more susceptible to environment inducing epigenetic alterations. One of the proposed mechanisms involved in placenta adaptation—in order to protect the offspring during perinatal exposure of EDCs is DNA methylation (John, 2017).

Interesting, BPA is elevated in lung cancer patients, especially past smokers; however, there is evidence that BPA may have come from other sources other than cigarettes (Pamungkas, Park, Lee, Jee, & Park, 2016). BPA at low concentration have high reactivity and selectivity for ER; oxidative enzymes from fungi such as laccases can oxidate BPA, turning this EDC into a much less reactive substance losing any ERα-dependent activity (Chairin et al., 2013).

The role of BPA to induce lung cancer independently of smoking history has been shown by X-ray studies and in vitro studies with lung cancer cells, where at very low concentrations of BPA, migration and invasion was stimulated via upregulation of MMP-2, which could enhance the susceptibility to carcinogenesis. Also, it was showed that BPA could the PPARy receptor. This ligand-activated transcription factor was found to induce differentiation and apoptosis in lung cancer cells so BPA promoted prevention of apoptosis resulting in the survival of cancer cells (Kim, Ahn, & Cheon, 2007; Zhang et al., 2014).

Studies on the long-term exposure to low doses of BPA and its metabolites, present in food, water or environmental carriers, results on an impact on the bone morphogenetic protein (BMP); this BMP belongs to the TGF-β superfamily, which is responsible for many regulatory systems, including in the nervous system, prostate, skin, intestine, ovary, and mammary gland (Yadin, Knaus, & Mueller, 2016). Indeed, pollutants could modify the physiological control of human epithelial SCs through BMPs; it was observed that BPA increased immature features and amplified the response of cells to BMPs (Huang et al., 2011). Furthermore, BPA is able to modulate the response of immature cells to BMPs, possibly by changing the expression and localization of type-1 BMP receptors, mechanism seen in different tumor types, particularly in breast and lung cancer (Dayde et al., 2016).

As mentioned above, BPA and phtalates are widely found in daily life and the tendency to bioaccumulation require special attention, above all during pregnancy and early life; this window is important because the epigenetic changes to protect the off spring can pass



**FIGURE 6** Effects of the exposure of EDs in critical periods of development related to the generation of different types of cancer. The exposure of EDCs at perinatal or neonatal stage impacts at different cells and tissue levels giving several epigenetic, genetic, and morphological changes. The majority of findings have been performed in animal models but they can be translated to humans due to the analog model hypothesis

transgenerationally. Importantly, avoidance of exposure to air pollution and changes in dietary can improve dramatically the effects of EDCs during pregnancy; simple changes like avoiding sodas and hamburgers, the use of proper cosmetic, and so forth could diminish urinary BPA concentration, and the related toxic effects on the offspring (Quiros-Alcalá et al., 2013).

Figure 6 depicts the hypothesis of the analogue model, which postulates that all findings in animal models, can be directly extrapolated to human health. However, it is clear that more research in humans is needed to be able to clearly demonstrate the detrimental effect of microplastics components, on human health, particularly in cancer.

## 16 | CONCLUSION

The existing scientific evidence in preclinical and clinical models about the exposure of bisphenols and phthalates at critical periods of the development on the immune system and the development of certain types of cancer was described. Although there are still no conclusive reports of the effect of these compounds in humans, it is

highlighted that the administration of them during critical stages of development affects important immune system components, and in some cases immune function; which might be related to the development of different diseases including cancer. What is clearer, is the fact that both kinds of EDCs affect rodent mammary gland development, that may be relevant to effects on humans. Thus far, the relationship between environmental and toxic chemicals is still controversial. In addition, it constitutes a great challenge to determine if a particular chemical, or a combination of them, is causing different types of cancer. Considering that the incidence of cancer has increased as countries have moved forward into industrialization, environmental toxic exposure constitutes a relevant public health concern worldwide.

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## CONFLICT OF INTEREST

The authors declare no conflict of interests.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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