Prenatal Exposure to Endocrine-Disrupting Chemicals and Asthma and Allergic Diseases

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Abstract

Endocrine-disrupting chemicals (EDCs) interfere with endogenous hormones and are present in many consumer products. In addition, they affect the development and functions of the immune system. The prenatal period is critical, because exposure to EDCs can induce irreversible changes in the immune system and increase susceptibility to asthma and allergies later in life. Nonpersistent EDCs are of most concern owing to their high annual production and potential toxicity. In this review, we summarize the literature on the effects of prenatal exposure to nonpersistent EDCs—phthalates and phenols—on asthma and allergic diseases, describe the underlying biological mechanisms, and make recommendations. Between 2011 and 2020, a total of 19 prospective studies were published. Most of these were focused on phthalates and bisphenol A and few on other bisphenols, parabens, triclosan, and benzophenone-3. Evidence remains insufficient owing to differences in chemical use between countries, sociodemographic characteristics of the study populations, misclassification of exposure due to the high within-subject variability, and heterogeneity in the definition of health outcomes. EDCs can alter airway cell differentiation and gut microbiota, shift the immune response towards T_H2, alter expression of T regulatory cells and T_H17, and weaken innate immunity. In order to better understand the burden of EDCs on the respiratory and immune systems, we require thoughtfully designed studies to assess exposure, appropriately characterize asthma and allergic phenotypes, and evaluate biological mechanisms and EDC mixtures. Research will help to implement public health policies that reduce exposure to EDCs in the community, particularly in pregnant women.

Key words: Endocrine disruptors. Pregnancy. Asthma. Eczema. Food allergy. Immune system.

Resumen

Los disruptores endocrinos (DEs), sustancias químicas que pueden interferir con las hormonas endógenas y que están presentes en muchos productos de consumo, pueden afectar el desarrollo y función del sistema inmune. El período prenatal es crítico porque su exposición puede inducir cambios irreversibles en el sistema inmunitario y aumentar la susceptibilidad al asma y alergias. Los DEs de mayor preocupación son los no persistentes por su alta producción y potencial toxicidad. En esta revisión, resumimos la literatura sobre los efectos de la exposición prenatal a DEs no persistentes (ftalatos y fenoles) sobre el asma y las alergias, describimos los mecanismos biológicos y desarrollamos recomendaciones. Entre 2011 y 2020, se publicaron un total de 19 estudios prospectivos. La mayoría se centraron en ftalatos y bisfenol A y pocos en otros bisfenoles, parabenos, triclosán y benzofenona-3. En general, la evidencia aún es insuficiente, probablemente debido a diferencias en el uso de químicos y las características sociodemográficas entre países, la clasificación errónea de la exposición y la heterogeneidad en la definición de los fenotipos. Los DEs pueden alterar la diferenciación celular de las vías respiratorias, cambiar la respuesta inmune hacia Th2, alterar la expresión de las células T reguladoras y Th17 y alterar la microbiota intestinal. Se necesitan estudios con buena medida de exposición y caracterización de los fenotipos y que consideren mecanismos biológicos y mezclas de DEs. Esta investigación contribuirá a la implementación de políticas de salud pública para reducir la exposición a los DEs en la comunidad, particularmente en mujeres embarazadas.

Palabras clave: Disruptores endocrinos. Embarazo. Asma. Eczema. Alergia alimentaria. Sistema inmune.

1. Introduction

The prevalence of asthma and allergic diseases has increased dramatically in recent decades, especially in children [1]. It is estimated that, on average, 12% of children around the world are affected by asthma, 9% by allergic rhinitis, and 22% by eczema [2-4]. These numbers vary considerably between regions, with the highest prevalence recorded in Northern European countries [2]. Food allergies are also common, affecting up to 10% of children [3,5,6]. In a recent population-based cohort of 1301 European children from the UK, France, Greece, Spain, Norway, and Lithuania (2013-2016, mean age: 8 years) [7], we reported a similar prevalence for asthma (12%), eczema (21%), and food allergies (10%), but a higher prevalence for allergic rhinitis (25%) (manuscript in preparation). Of interest, these symptoms often co-occur in the same individual (multimorbidity), more commonly than expected by chance [4].

The reasons for the increased prevalence of asthma and allergic diseases have not been well established. Although these diseases have a genetic component, the rapid increase cannot only be due to changes in the underlying genetic susceptibility of the population [8]. Changes in lifestyle and in the environment are believed to play a key role in allergic diseases, particularly during early stages of development. Indeed, the fetal period is a critical window for the development of the immune system owing to the immaturity of fetal organ systems and undeveloped detoxification processes. Exposure to a harmful environment during this period can induce irreversible changes in the immune system and increase susceptibility to asthma and allergic diseases later in life [9]. This observation is consistent with the Developmental Origins of Health and Disease (DOHaD) approach [10], which states that early-life factors may have a long-term impact on disease in adulthood.

Many early-life lifestyle and environmental factors have been reported to contribute to the development of respiratory and allergic diseases, including maternal atopy/asthma, inadequate diet during pregnancy, tobacco smoke, pre-pregnancy obesity, psychological distress, low birth weight, rapid infant growth, and viral respiratory infections [11-13]. Among environmental exposures, air pollution caused by traffic has been widely studied, and it is estimated that 4 million new cases of pediatric asthma are attributable to nitrogen dioxide pollution annually [14,15]. More recently, concern has been growing over the impact of environmental chemicals on onset of asthma and allergic diseases. Endocrine-disrupting chemicals (EDCs) in particular have gained attention owing to their capacity to affect the development and function of the immune system [16].

2. Endocrine-Disrupting Chemicals

EDCs are natural or synthetic chemicals that can interfere with the synthesis, secretion, binding, transport, and metabolism of endogenous hormones involved in regulating developmental processes [17]. Synthetic EDCs are produced in large quantities worldwide and used in many consumer goods. Millions of tons of synthetic chemicals are produced every year (>300 million tons consumed in Europe in 2018 [18]) and many are suspected or proven EDCs. Reported figures vary from 86 included in the REACH Regulation of the European Chemicals Agency (ECHA) [19] to 1482 included in The Endocrine Disruption Exchange (TEDX) list [20]. However, the exact number of EDCs in marketed products is unknown, as there are no common criteria for labelling a chemical as an EDC [21,22]. EDCs include historical persistent organic pollutants (eg, dioxins), polychlorinated biphenyls (PCBs), and pesticides (eg, dichlorodiphenyltrichloroethane [DDT], which was banned), as well as emerging persistent and nonpersistent compounds such as per- and polyfluoroalkyl substances (PFASs), phenols (eg, bisphenol A [BPA], parabens), and phthalates. Emerging compounds are particularly concerning owing to their high annual production and potential toxicity.

Human populations are continuously exposed to EDCs through food (pesticides), food packaging (phenols, phthalates), cosmetics (parabens, phthalates), dust inhalation (phthalates), and consumer goods (phthalates in paints, PFASs in nonstick cookware). Human exposure to EDCs is widespread, as observed in many human biomonitoring studies [23-25]. Of concern, exposure to these chemicals is considerable in pregnant women and children, with most compounds being detected in more than 90% of body fluids [25-27]. Infants and young children generally present higher levels than adults because they lack specific detoxification pathways and are exposed via other channels, such as breastfeeding and crawling. Most compounds can also cross the placental barrier. Although some European countries (eg, France) have started to ban the marketing of certain EDCs, such as BPA, new compounds with endocrine-disrupting capacity are continuously being produced, and their potential toxicity is unknown. Indeed, the 7th EU Environment Action Programme, which is committed to the development of a nontoxic environment by 2020 [28], was developed in response to emerging issues related to the growing presence of chemicals in everyday life. In addition, the current EU Commission has presented the "The European Green Deal", which aims for a nontoxic environment by 2050.

Given the activity of EDCs, exposure in vulnerable time periods (ie, prenatal life) can induce changes in organ and tissue development, with adverse effects occurring in the short and long terms, such as obesity and metabolic disorders, male and female reproductive disorders, reproductive cancers, thyroid disorders, neurodevelopmental delay, and IQ loss [21]. Exposure to EDCs has been estimated to cost the EU $163 billion in disease and dysfunction across the course of a lifetime [29]. EDCs can also disrupt the development and functioning of the immune and respiratory systems. For persistent EDCs, the evidence of their effects on respiratory health is moderate [30], whereas for nonpersistent EDCs it is inadequate [31]. In this review, we summarize current knowledge about the effects of prenatal exposure to nonpersistent EDCs, namely, phthalates and phenols (bisphenols, parabens, triclosan, and benzophenone-3), on asthma and allergic diseases, and discuss potential biological mechanisms. We also develop recommendations for future studies.

3. Phthalates

Phthalates are a group of phthalic acid diester compounds with straight or branched chain alcohols that are generally used as plasticizers to add flexibility to plastic consumer products. Around 6-8 million tons of phthalates are consumed every year [32]. Phthalates are divided into long-chain phthalates, such as di-2-ethylhexyl (DEHP), butylbenzyl (BBzP), and di-isononyl (DiNP) phthalates, and short-chain phthalates such as di-ethyl (DEP) and di-n-butyl (DnBP) phthalates. Long-chain phthalates are widely used in polyvinyl chloride (PVC) applications and are present in building materials, food containers, and many other consumer products. Short-chain phthalates are further used in non-PVC products including adhesives and personal care products. Phthalates are not chemically bound to other substances and can therefore be easily released into the air or leached from plastic, leading to food and environmental contamination [33]. Whereas food is considered to be the major source of exposure for long-chain phthalates, personal care products and indoor air may be an important source of exposure for short-chain phthalates. In 1999, the EU banned the use of 3 phthalates (ie, DEHP, dibutyl phthalate [DBP], and benzyl butyl phthalate [BBP]) in the manufacture of toys and childcare articles. In 2011, these 3 phthalates and diisobutyl phthalate (DiBP) were added to the REACH candidate list owing to their suspected reproductive toxicity [34].

3.1. Mechanisms

Phthalates have been reported to have estrogenic, antiestrogenic, and antiandrogenic effects depending on the congener and metabolite analyzed. For instance, DEHP seems to have estrogenic activity, whereas monobenzyl phthalate (MBzP), a metabolite of BBzP, seems to have antiestrogenic activity. Further studies are needed to clarify the various activities of phthalate compounds [35,36]. Because of their potential endocrine-disrupting activity, some phthalates (eg, DEHP, DiNP, diisodecyl phthalate [DiDP]) have been reported to bind the peroxisome proliferator-activated receptor γ (PPARγ) [37,38]. In the case of DEHP, this interaction with PPARγ alters airway cell differentiation and surfactant protein production in the lungs, thus explaining the potential association between DEHP and asthma [39]. It is not clear whether phthalates increase inflammatory responses [40]. However, what seems to be more consistent, according to animal and in vitro studies, is that several phthalates can have adjuvant effects on type 2 helper T cell (T_H2) differentiation and influence antibody response, thus affecting the adaptive immune system [40,41]. Other studies have also reported alterations of the innate immune system, such as increased production of tumor necrosis factor α (TNF-α) by macrophages, and reduced capacity for migration of these cells [16].

3.2. Current Evidence From Birth Cohort Studies

In the first epidemiological studies on phthalates and respiratory health, exposure was assessed by measuring home dust phthalate levels or by counting the number of rooms with PVC flooring [42]. We only took into consideration studies that assessed exposure to phthalates using biomarkers; a total of 13 studies have been published to date (Table). In 2017, Li et al [42] performed a systematic review and meta-analysis including 5 [43-47] of these 13 studies, and observed that prenatal exposure to MBzP was associated with an increased risk of asthma. Since this systematic review, a further 8 studies have been published [48-55]. In 2 cohorts, in utero exposure to long-chain phthalates and DiDP and DiNP metabolites was associated with an increased risk of bronchiolitis/bronchitis, wheezing, and asthma [49,53]. These findings are relevant, because DiDP and DiNP are increasingly used as DEHP substitutes and are the most commonly used plasticizers in Western Europe [56,57]. Recently, in another cohort, exposure to MBzP from pregnancy until 9 years of age was associated with an increased risk of wheezing and asthma in children; however, the study did not separately assess the effects of prenatal and postnatal exposures [54]. In contrast, a decreased risk of wheezing was associated with prenatal exposure to metabolites of DEP and DnBP [51]. Regarding allergic disorders, exposure to metabolites of DiNP and DiBP was associated with an increased risk of eczema [50], and, among sensitized boys, exposure to metabolites of DiBP and DBP increased the risk of ever eczema [50]. Food allergies have been assessed in only 1 cohort, in which the authors observed that prenatal exposure to MBzP increased the risk of food allergy [55]. The same cohort also found an association between DEHP metabolites and increased risk of food allergies and lower risk of atopic dermatitis; however, no difference was made between prenatal and postnatal exposures in the models [54]. Finally, 2 studies explored the link between phthalates and immune biomarkers: one study found an association between a DnBP metabolite and higher T_H2 percentage in children younger than 5 years [52], whereas the other did not find any association with immune markers measured in cord blood [48].

4. Phenols

4.1 Bisphenols

Bisphenols are used in the manufacture of plastic polymers, such as polycarbonate plastics and epoxy resins. Diet represents the main source of exposure. The most widely known, produced, and used bisphenol is BPA, whose global production in 2015 was estimated at 5.4 million tons [58]. BPA was first reported to be an EDC in the late 1930s and was recently formally identified as an EDC by the European Chemicals Agency (ECHA). Owing to concern over effects on neurodevelopment and other toxic effects, the EU banned BPA in baby bottles in 2011 [59], and its use has recently been restricted in thermal paper [60]. Consequently, chemical companies have started to generate other molecules to replace BPA, such as bisphenol S (BPS) and bisphenol F (BPF). However, these molecules have similar properties to BPA and are suspected of having similar toxicity [61].

4.1.1. Mechanisms

BPA is estrogenic and binds to estrogen receptors α and β, with approximately 10-fold higher affinity for the β receptor

Table. Studies on Prenatal Exposure to Nonpersistent Endocrine-Disrupting Chemicals and Asthma and Allergic Diseases (Ordered by Year and Author)

Author (Year)	Country (Cohort Name)	Years of Recruitment	No.	Child's Age[a]	Exposure Assessment	Outcomes Assessment		Statistically Significant Main Findings
						Method	Symptoms	
Phthalates								
Just et al (2012) [43]	US (CCCEH)	1999-2006	407	3-60 mo	1 urine	ISAAC, IgE	Itchy rash, eczema, allergic sensitization	MBzP ↑ eczema
Gascon et al (2014) [45]	Spain (INMA)	2004-2006	462	1.5-7 y	2 urines	ISAAC, IgE	Chest infections, bronchitis, wheeze, asthma, eczema, atopy	DEHP ↑ chest infections, bronchitis, wheeze, asthma MBzP ↑ wheeze, asthma
Smit et al (2014) [46]	Ukraine, Poland, Greenland (INUENDO)	2002-2004	1024	5-9 y	1 serum sample	ISAAC	Wheeze, asthma, eczema	DiNP metab ↓ eczema
Whyatt et al (2014) [44]	US (CCCEH)	1998-2006	300	5-11 y	1 urine	ISAAC, BRQ, physician examination	Asthma	MBzP, DnBP metabolism ↑ asthma
Ashley-Martin et al (2015) [48]	Canada (MIREC)	2008-2011	1258	Birth	1 urine	IgE, IL-33, thymic stromal lymphopoietin	–	–
Ku et al (2015) [47]	Taiwan (Taiwan Maternal and Infant Cohort Study)	2000-2001	171	8 y	1 urine	ISAAC, IgE	Wheeze, asthma	MBzP ↑ wheeze (only boys) DEHP metabolism ↑ IgE
Stelmach et al (2015) [55]	Poland (REPRO_PL)	2007-2011	147	2 y	1 urine	ISAAC, physician examination	Wheeze, atopic dermatitis, food allergy	MBzP ↑ food allergy
Berger et al (2018) [52][b]	US (CHAMACOS)	1999-2000	392	2-7 y	2 urines	ISAAC, T_H1/T_H2 cells	Asthma, eczema, aeroallergies	DnBP metabolism ↑ T_H2
Buckley et al (2018) [51]	US (Mount Sinai Children's Environmental Health Study)	1998-2002	164	6-7 y	1 urine	ISAAC	Wheeze, asthma, atopy	DEP metab, DnBP metabolism ↓ wheeze (only girls)
Soomro et al (2018) [50]	France (EDEN – only boys)	2003-2006	587	1-5 y	2 urines	ISAAC, IgE	Eczema, atopy	DiNP and DiBP metabolism ↑ eczema DBP and DiBP metabolism ↑ eczema (only IgE-sensitized boys)
Vernet et al (2018) [49]	France (EDEN – only boys)	2003-2006	587	1-5 y	2 urines	ISAAC	Bronchiolitis/bronchitis, wheeze, asthma	DiDP metabolism ↑ wheeze[c] DiNP metabolism ↑ bronchiolitis/bronchitis[b]
Berger et al (2019) [53][c]	US (CHAMACOS)	1999-2000	392	2-7 y	2 urines	ISAAC, T_H1/T_H2 cells	Asthma, eczema, aeroallergies	DiNP ↑ asthma
Podlecka et al (2020) [54]	Poland (REPRO_PL)	2007-2011	145	9 y	1 urine	ISAAC, physician examination	Wheeze, asthma, eczema, allergic rhinitis, atopic dermatitis, food allergy	DEHP metabolism ↑ food allergy, ↓ atopic dermatitis MBzP, DEHP metabolism ↑ wheeze, asthma

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(Continuation)

Author (Year)	Country (Cohort Name)	Years of Recruitment	No.	Child's Age[a]	Exposure Assessment	Outcomes Assessment Method	Outcomes Assessment Symptoms	Statistically Significant Main Findings
Bisphenols								
Spanier et al (2012) [74]	US (HOME)	2003-2006	398	0-3 y	2 urines	Questionnaires	Wheeze	BPA ↑ wheeze
Donohue et al (2013) [77]	US (CCCEH)	1998-2006	568	5-12 y	1 urine	ISAAC, IgE, physician examination, FeNO	Wheeze, asthma	BPA ↓ wheeze
Gascon et al (2014) [45]	Spain (INMA)	2004-2006	462	1.5-7 y	2 urines	ISAAC, IgE	Chest infections, bronchitis, wheeze, asthma, eczema	BPA ↑ chest infections, bronchitis, wheeze, asthma
Spanier et al (2014) [76]	US (HOME)	2003-2006	398	0-5 y	2 urines	Questionnaires	Wheeze	BPA ↑ wheeze
Ashley-Martin et al (2015) [48]	Canada (MIREC)	2008-2011	1258	Birth	1 urine	IgE, IL-33, thymic stromal lymphopoietin	–	–
Zhou et al (2017) [78]	China	2012-2014	412	6 mo	1 urine	ISAAC	Wheeze, itchy rash, eczema	BPA ↑ allergic diseases (only girls)
Buckley et al (2018) [51]	US (Mount Sinai Children's Environmental Health Study)	1998-2002	164	6-7 y	1 urine	ISAAC	Wheeze, asthma, atopy	BPA ↑ asthma (only boys)
Vernet et al (2018) [49]	France (EDEN – only boys)	2003-2006	587	5 y	2 urines	ISAAC	Bronchiolitis/bronchitis, wheeze, asthma	BPA ↑ bronchitis/bronchiolitis, asthma
Berger et al (2019) [53]	US (CHAMACOS)	1999-2000	392	2-7 y	2 urines	ISAAC, T_H1/T_H2 cells	Asthma, eczema, aeroallergies	–
Parabens								
Berger et al (2018) [52]	US (CHAMACOS)	1999-2000	392	2, 5, and 7 y	2 urines	ISAAC, T_H1/T_H2 cells	Asthma, eczema, aeroallergies	Propylparaben ↓ asthma Methylparaben ↓ T_H1, T_H2
Vernet et al (2018) [49]	France (EDEN – only boys)	2003-2006	587	5 y	2 urines	ISAAC	Bronchiolitis/bronchitis, wheeze, asthma	Ethylparaben ↑ asthma
Lee-Sarwar et al (2018) [84]	US (VDAART randomized clinical trial)	2009-2011	467	3 y	2 pooled plasma samples	Questionnaires, IgE	Wheeze, asthma, allergic sensitization	Propylparaben ↓ allergic sensitization (only girls)

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(Continuation)

Author (Year)	Country (Cohort Name)	Years of Recruitment	No.	Child's Age[a]	Exposure Assessment	Outcomes Assessment Method	Outcomes Assessment Symptoms	Statistically Significant Main Findings
Triclosan								
Ashley-Martin et al (2016) [86]	Canada (MIREC)	2008-2011	1219	Birth	1 urine	IgE, IL-33, thymic stromal lymphopoietin	–	–
Berger et al (2018) [52]	US (CHAMACOS)	1999-2000	392	2, 5, 7 y	2 urines	ISAAC, T_H1/T_H2 cells	Asthma, eczema, aeroallergies	–
Buckley et al (2018) [51]	US (Mount Sinai Children's Environmental Health Study)	1998-2002	164	6-7 y	1 urine	ISAAC	Wheeze, asthma, atopy	–
Lee-Sarwar et al (2018) [84]	US (VDAART randomized clinical trial)	2009-2011	467	3 y	2 pooled plasma samples	Questionnaires, IgE	Asthma, wheeze, allergic sensitization	↓ wheeze, asthma (only girls)
Vernet et al (2018) [49]	France (EDEN – only boys)	2003-2006	587	5 y	2 urines	ISAAC	Bronchiolitis/bronchitis, wheeze, asthma	–
Benzophenone-3								
Buckley et al (2018) [51]	US (Mount Sinai Children's Environmental Health Study)	1998-2002	164	6-7 y	1 urine	ISAAC	Wheeze, asthma, atopy	↓ wheeze (only girls)
Berger et al (2018) [52]	US (CHAMACOS)	1999-2000	392	2, 5, 7 y	2 urines	ISAAC, T_H1/T_H2 cells	Asthma, eczema, aeroallergies	–

Abbreviations: BPA, bisphenol A; BRQ, Brief Respiratory Questionnaire; CCCEH, Columbia Center for Children's Environmental Health Cohort; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DBP, dibutyl phthalate; DEHP, di-2-ethylhexyl phthalate; DEP, di-ethyl phthalate; DiBP, di-isobutyl phthalate; DiDP, di-isodecyl phthalate; DiNP, di-isononyl phthalate; DnBP, di-n-butyl phthalate; EDEN, Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant; FeNO, fraction of exhaled nitric oxide; HOME, Health Outcomes and Measures of the Environment; IgE, immunoglobulin E; INMA, INfancia y Medio Ambiente (Environment and Childhood); INUENDO, Human Fertility at Risk from Biopersistent Organochlorines in the Environments; ISAAC, International Study of Asthma and Allergies in Childhood; MBzP, monobenzyl phthalate (metabolite of utylbenzyl phthalate (BBzP)); MIREC, Maternal-Infant Research on Environmental Chemicals; REPRO_PL, Polish Mother and Child Cohort Study; VDAART, Vitamin D Antenatal Asthma Reduction Trial.

[a]At the time of outcome assessment.

[b]Phthalate metabolites differ between studies.

[c]All results were borderline statistically significant.

[62]. It also binds to androgen and progesterone receptors, PPAR, and the aryl hydrocarbon receptor, a ligand-dependent transcription factor present in almost every tissue [63,64]. In fact, some studies have observed that BPA can stimulate cellular responses at concentrations below the levels where it is expected to bind to the classic nuclear ERs [65,66]. It also binds to the thyroid hormone receptor, inhibiting the transcriptional activity stimulated by triiodothyronine (T3) [64]. This endocrine-disrupting activity explains the immunomodulatory properties of BPA observed in animal and in vitro models [63,64,67,68], as in humans [69]. The immune effects observed in relation to BPA exposure include T_H1/T_H2 cell shifts, reduction in T regulatory (Treg) cells (which are important in controlling proinflammatory reactions), T_H17 alterations (T_H17 are involved in the pathogenesis of various autoimmune and inflammatory diseases), reduced innate immunity, increased B-cell count and activity, and increased oxidative stress and expression of immunity-related genes [63,64,70]. Altered airway cells in rhesus macaques have also been reported [71].

4.1.2. Current evidence from birth cohort studies

Studies conducted to date on the effects of exposure to bisphenols during fetal life on asthma and allergic diseases have focused on BPA (Table). To our knowledge, only 1 study has assessed the influence of BPS and BPF on asthma and hay fever using data from 3500 persons aged 12 years or older participating in the National Health and Nutrition Examination Survey (NHANES) for 2013-2016 [72]. In this cross-sectional study, BPS and BPF were associated with increased odds of current asthma [72]. Regarding the effects of in utero exposure to BPA, a systematic review of cohort studies conducted in 2016 [73] identified 3 studies showing an association between prenatal exposure to BPA and increased risk of childhood wheeze, chest infections, bronchitis, and asthma [74-76], whereas 1 study reported a decreased risk of wheeze [77]. This systematic review was followed by a further 5 studies [48,49,51,53,78]. Three reported an increased risk of asthma, lower respiratory tract infections, and allergic diseases (ie, itchy rash and eczema) associated with prenatal exposure to BPA [49,51,78], whereas 2 reported no association with asthma, aeroallergies, eczema, or immune markers such as immunoglobulins, interleukins, and T_H1 and T_H2 cytokine-producing cells [48,53]. Sex-specific effects were identified in only 2 studies with inconsistent results: one reported a higher risk of allergic diseases among girls [78], and the other reported a higher risk of asthma among boys [51].

4.2 Parabens

Parabens are alkyl esters of p-hydroxybenzoic acid with antifungal and antibacterial properties. They are frequently used as preservatives in cosmetic products, toiletries, foods, and pharmaceuticals. The most common are methyl-, ethyl-, propyl-, and butylparaben, which are used alone or in the form of a mixture to increase their efficacy. Parabens enter the human body mainly through ingestion or skin absorption, although they are also present in dust and indoor air. Their production has increased rapidly in recent decades. In the early 2000s, it is estimated that parabens were present in more than 90% of cosmetic products [79]. Given their cytotoxicity and endocrine-disrupting properties, the EU restricted the use of parabens as preservatives in cosmetic products, with limits of 0.4% for a single ester and 0.8% for a mixture of parabens [80].

4.2.1. Mechanisms

The antimicrobial activity of these compounds could be altering microbiota in the gut (or other body sites) and shifting the $CD4^+$ response towards a T_H2 response, which is associated with allergy, eczema, and other diseases [81]. In fact, a study conducted in 2012 in almost 900 schoolchildren in the USA observed that concentrations of parabens were associated with increased levels of immunoglobulin E (IgE) [82]. However, appropriate data on prenatal exposure are lacking. In addition, parabens of long alkyl chains (eg, decylparaben) induce the release of histamine [16]. For instance, heptylparaben, another long-alkyl-chain paraben used as a food additive, has been reported to induce a strong allergic reaction on animal skin [83]. Other research has shown genotoxic and cytotoxic effects of parabens on human lymphocytes in vitro and their capacity to suppress immune response [83].

4.2.2. Current evidence from birth cohort studies

A total of 3 cohort studies, all published in 2018, evaluated the effect of prenatal exposure to parabens and asthma and allergic outcomes in offspring (Table). Two observed a decreased risk of asthma [52] and allergic sensitization associated with exposure to propylparaben (only in girls in the second study) [84], and a lower percentage of T_H1 and T_H2 cells associated with exposure to methylparaben [52]. On the contrary, one study, which only included boys, observed an increased risk of asthma following exposure to ethylparaben [49].

4.3 Triclosan

Triclosan is widely used as an antimicrobial agent and preservative in cosmetics, personal care products (eg, toothpaste), detergents, and other household cleaning products. Ingestion and dermal absorption are the main routes of exposure. Of interest, the chemical structure of triclosan is similar to that of PCBs, BPA, dioxins, and thyroid hormones [85]. In 2002, the worldwide production of triclosan exceeded 1500 tons per year [85]. Although the use of triclosan is not highly regulated, in light of mounting evidence on potential health effects, some companies have decided to remove triclosan from their products.

4.3.1. Mechanisms

As with parabens, the antimicrobial activity of triclosan may alter human microbiota and shift the immune response towards T_H2 [81]. Savage et al [82] also showed higher IgE levels in a population of school-aged children who were increasingly exposed to triclosan. However, as commented on below, relevant data on prenatal exposure are lacking. In addition, triclosan can inhibit the lytic function of natural-killer cells (NK) and mast cell degranulation and affect autophagy (an intracellular process that delivers the cargo,

including pathogens, to lysosomes for degradation) of specific macrophages (RAW264.7 cells) [16].

4.3.2. Current evidence from birth cohort studies

To date, 5 cohort studies have assessed whether fetal exposure to triclosan increases the risk of asthma and allergies in childhood (Table). Four did not observe any association between prenatal exposure to triclosan and asthma, wheezing, eczema, atopy, or immune biomarkers [49,51,52,86]. The fourth study reported a decreased risk of asthma and wheeze, but only in girls [84].

4.4 Benzophenone-3

Benzophenone-3, or oxybenzone, is a phenolic compound that is frequently used as an ultraviolet filter in sunscreen and as a fragrance enhancer in personal care products. Benzophenone-3 is one of the most widely used benzophenones for UV filters. Other benzophenones include benzophenone-1, which is used as a UV stabilizer in plastic surface coatings on food packages. Dermal and oral routes are the main sources of exposure. Benzophenone-3 is lipophilic and can accumulate in human and animal tissues [87]. It is estimated that 10 000 tons of UV filters are produced annually for the global market [87]. In 2017, the EU regulated the use of benzophenone-3 as a UV filter in up to 6% of cosmetic sunscreens and in up to 0.5% of cosmetic products [88].

4.4.1. Mechanisms

There is very limited information on the potential mechanisms by which benzophenone-3 increases the risk of allergic diseases and asthma. As with the previous compounds analyzed, a recent review suggests that it could stimulate the differentiation of T cells towards a T_H2 response [16]. However, further animal and in vitro studies are needed to better understand the potential mechanisms involved.

4.4.2. Current evidence from birth cohort studies

Only 2 studies have evaluated the potential effects of benzophenone-3 on asthma and allergic diseases in childhood (Table). One showed a lower risk of wheezing among girls [51], whereas the other did not observe any associations [52].

5. State of the Art and Future Research

In this review, we present updated evidence of the effects of exposure to phthalates and phenols during pregnancy on the development of asthma and allergic diseases in childhood. Although the number of studies on phthalates and BPA is quite extensive, they are still subject to inconsistencies. For triclosan, parabens, and benzophenone-3 in particular, the number of studies is very limited. Consequently, the potential effects of EDCs on immune and respiratory health are not taken into consideration when estimating their burden [29]. Indeed, their burden is calculated only by assessing the effects on obesity, diabetes, reproductive disorders, IQ loss, and behavioral problems [29]. Of relevance, although the EU recently funded 12 projects to improve the identification of EDCs [89] (call SC1-BHC-27-2018), none consider the effects on respiratory or immune health for their identification. Given the scarcity of studies and their inconsistent results, further work is needed to elucidate the role of EDCs in asthma and allergies.

Discrepancies across studies may reflect differences in chemical use between countries and/or in sociodemographic characteristics of the populations. The fact that most studies have small samples (fewer than 600) may hinder the identification of most vulnerable subgroups (eg, according to sex, sociodemographic characteristics, preterm births). Inconsistencies between studies may also be due to the nonmonotonic dose-response curves associated with exposure to EDCs (ie, low doses can have more potent effects than higher doses) [90]. Combining data from different birth cohorts can lead to more conclusive results, as well as to a more robust analysis, including effect modifiers and adequate modelling of the exposure-response relationship [91,92]. In most cohorts, pregnant women were recruited more than a decade ago (Table), and newer EDCs could not be detected at that time. For example, in the INMA cohort [45], where pregnant women were recruited between 2004 and 2006, BPS was not detected in most of the maternal urine samples (unpublished results). Although the structure and mechanisms of action of new substitutes are similar to those of the initial ones and we therefore expect that they would have similar health effects, their potential toxicity can only be assessed in recently established population-based studies. Finally, it is important to consider that we have not reviewed the literature on exposure to currently used pesticides (eg, organophosphate pesticides), glycol ethers, and polycyclic aromatic hydrocarbons (PAHs), which can also have an endocrine-disrupting effect and thus lead to asthma and allergies.

5.1 Improving Exposure Assessment

Because we expect effect sizes associated with exposure to EDCs to be small, a reliable exposure assessment is needed to assess the effects of these compounds on respiratory and immune health. All cohort studies but 2 determined the levels of phthalates and phenols in spot urine samples collected during pregnancy (Table). Two cohorts [46,84] used maternal serum or plasma to assess exposure to these nonpersistent EDCs. On ingestion, phthalates and phenols are metabolized rapidly and excreted in urine after a few hours or days. A low proportion are retained in blood, and circulating levels are usually lower than urinary levels; hence, assessment of urinary levels is the preferred option [93]. However, given that EDCs are excreted quickly in urine, concentrations determined in a spot urine sample only reflect exposure for a short period of time. Substantial measurement error, such as that occurring when a limited number of urine samples are taken to characterize long-term exposure, can result in attenuated associations in analyses linking an exposure with a health outcome if the error in the assessment is random and consequently not associated with the outcome (nondifferential) [94]. It is estimated that in the case of compounds with very high within-subject variability, such as BPA, attenuation bias (underestimation of the effects) can reach 80% [95]. Recently, new sampling strategies have been postulated to limit misclassification of exposure by pooling several urine samples per subject [95,96]. This

pooling approach is logistically feasible and does not increase analytical costs since only 1 urine pool is eventually analyzed [96]. We demonstrated that this is a valid approach for most phthalates and phenols, but not for other substances such as organophosphate pesticides, to which we are intermittently exposed (in this case, more than 40 urine samples are required during pregnancy [96]). Levels of the most variable compounds can be alternatively determined in hair samples with much lower within-subject variability than urine concentrations [97], as this approach reflects long-term exposure. Another alternative, is the use of personal silicone wristbands as passive samplers [98]; these also provide information on long-term exposure and correlate well with metabolites in urine for some compounds, such as PAHs [99].

5.2 Improving Assessment of Asthma and Allergic Phenotypes

Proper characterization of asthma and allergy phenotypes is required to adequately identify underlying environmental causes. Almost all the studies reviewed collected information on asthma and allergic symptoms using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire administered to the mothers (Table). The use of standardized questionnaires enables results to be compared across studies, although they can be subject to under- or over-reporting of the symptoms, which may lead to attenuation or overestimation of the results. This can be solved by considering information on symptoms collected at multiple time points during childhood, as was the approach in some studies [44,45], or by a physical examination of children with respiratory symptoms, as was the case in the Columbia Center for Children's Environmental Health Cohort (CCCEH) [77]. However, we recognize that this is not always possible. Allergy can be better diagnosed by performing a skin prick test, measurement of fractional exhaled nitric oxide (FeNO), or measurement of IgE levels, as in some cohorts (Table). Given the heterogeneity of asthma and allergic phenotypes, there is no uniform set of diagnostic criteria, and definitions vary according to the study. In the CCCEH cohort, for example, allergists and pediatric pulmonologists defined asthma based on current asthma-related symptoms and medication, the postbronchodilator test result, and a history of asthma on previous questionnaires [77], whereas in INMA [45] we defined asthma following the MeDALL recommendations [100], which take into account questions on physician-based diagnosis, asthma treatment, and wheezing symptoms. Nevertheless, we should also consider that although a physician-based diagnosis provides more reliable information than parent-reported respiratory symptoms, variations in the prevalence of asthma and allergic diseases between countries may reflect differences in diagnostic criteria (readily diagnosed in some countries while unrecognized in others) [58]. Future studies assessing the effects of prenatal exposure to EDCs on asthma and allergy should include a better characterization of asthma and allergic phenotypes by considering alternative tests and the course of respiratory symptoms [101], assessing food allergy (since only 1 study has assessed it), and following up children at later ages (children were younger than 11 years in all studies) to elucidate whether the effects of early-life exposure to EDCs persist into adolescence and adulthood. Moreover, we recommend taking multimorbidity into consideration, since it has been shown that asthma and allergic diseases co-occur more often than expected by chance [4] and that they may coexist with other diseases that have also been associated with EDCs [21], such as other respiratory problems (eg, impaired lung function) [102], cardiovascular and metabolic diseases [103], and some mental health disorders (eg, attention-deficit/hyperactivity disorder) [104].

5.3 Assessing Mixtures of EDCs

Humans are exposed to multiple EDCs simultaneously, and it is important to understand how these multiple compounds interact and which EDCs are the most toxic in relation to asthma and allergy. Most of the studies included in this review assessed a single EDC at a time. Some studies adjusted the models for another EDC (eg, [44,45]), while Smit et al [46] considered many EDCs simultaneously (phthalates, perfluoroalkyl compounds, DDT metabolites, and PCBs). In order to address the high correlation between these chemicals, the authors applied a dimension reduction method—principal component analysis—to transform a number of correlated variables into a smaller number of uncorrelated principal components [105]. However, exposure to multiple EDCs can result in synergistic, antagonistic, or cumulative effects (for compounds acting via similar pathways) [106,107]. There is substantial toxicological evidence that mixtures are often more toxic than the individual compounds [106,108]. For example, using data from the CCCEH cohort, Whyatt et al [109] tested the interaction between maternal phthalate levels and child BPA levels and observed that the association between BPA and respiratory outcomes was present only among those children whose mothers had high levels of MBzP during pregnancy. Studying the health effects of exposure to combinations of EDCs requires an assessment of the potential for interaction between copollutants and for confounding between exposures, as well as a careful consideration of the biological mechanisms and modes of action involved [17,106,110]. New statistical tools to estimate the effect of multipollutant mixtures are being developed, particularly within the framework of exposome research [105,111]. Although research on exposure to multiple EDCs has just started, international bodies such as the World Health Organization already recognized the need to include mixtures in the assessment of chemical risk and for purposes of regulation [108,112].

5.4 Exploring the Biological Mechanisms

Understanding the biological pathways through which EDCs can increase the risk of asthma and allergies is key to establishing a causal inference. Studies performed to date show that EDCs can affect the development, functions, and lifespan of immune cells [16]. EDCs can also increase the risk of asthma and allergies through epigenetic changes (eg, alterations of DNA methylation) [113,114]. However, epigenetic studies require large samples to achieve optimal statistical power and various populations to replicate the findings in order to reduce false-positive results. The international Pregnancy And Childhood Epigenetics (PACE) Consortium, which includes 39 studies with DNA methylation data, provides an excellent opportunity to address this issue [115]. Another potential

mechanism that is just starting to be studied is changes in gut microbiota; the gut microbiome and the immune system develop in parallel and with strong crosstalk throughout life. Some EDCs have been reported to worsen gut dysbiosis in animal models, and this is thought to be associated with immune alterations [116-118]. It would be particularly interesting to study the effect of compounds that are specifically designed to exercise an antimicrobial effect (eg, triclosan and parabens) [81].

6. Conclusion

Exposure to EDCs during vulnerable periods can disrupt the development and functioning of the immune and respiratory systems and increase the risk of asthma and allergic diseases in children. In this review, we summarized current evidence for the effects of prenatal exposure to phthalates and phenols on respiratory outcomes and allergies and concluded that the evidence is still insufficient. In order to better understand the burden of EDCs on the respiratory and immune systems, we require thoughtfully designed studies to assess exposure, appropriately characterize asthma and allergic phenotypes, and evaluate biological mechanisms and EDC mixtures. Research will help us to implement public health policies to reduce exposure to EDCs in the community, particularly in pregnant women. EDCs are not covered efficiently in current EU regulations on chemicals (registration, evaluation, authorization, and restriction), additives, and cosmetics [21]. Given the widespread exposure to EDCs and their potential toxicity, the application of the precautionary principle (ie, act to address potential harmful issues without complete scientific certainty) would be the best approach, particularly if we are to protect the most vulnerable groups such as pregnant women and children. EU chemical legislation, which is currently dominated by a substance-by-substance approach, should move towards avoiding entire chemical classes (ie, specific hazard regulations) instead of individual compounds.

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Conflicts of Interest

The authors declare that they have no conflict of interests.

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