Prenatal exposure to endocrine disrupting chemicals and asthma and allergic diseases

**Short running title:** EDCs exposure and asthma and allergies

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Summary

Endocrine-disrupting chemicals (EDCs), chemicals that can interfere with endogenous hormones and that are present in many consumer products, can 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 the susceptibility of asthma and allergies later in life. Non-persistent EDCs are of most concern due to their high annual production and potential toxicity. In this review, we summarize the literature on the effects of prenatal exposure to non-persistent EDCs, namely phthalates and phenols, on asthma and allergic diseases, describe the biological mechanisms, and develop recommendations. Between 2011 and 2020, a total of 19 prospective studies were published. Most of them were focused on phthalates and bisphenol A and few on other bisphenols, parabens, triclosan, and benzophenone-3. Overall, the evidence is still insufficient due to differences in chemicals use between countries, sociodemographic characteristics of the populations, exposure misclassification due to the high within-subject variability, and heterogeneity on health outcome definitions. EDCs can alter airway cell differentiation, shift immune response towards Th2, alter T regulatory and Th17 expression, reduce innate immunity, and alter gut microbiota. Studies with a thoughtful exposure assessment design, a good characterization of the asthma and allergic phenotypes, and which consider biological mechanisms and EDCs mixtures are needed to better understand the burden of EDCs on the respiratory and immune systems. This research will contribute to implement public health policies to reduce EDCs exposure 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

Prevalence of asthma and allergic diseases has increased dramatically in the last decades and especially in children [1]. It is estimated that in average 12% of children around the world are affected by asthma, 9% are affected by allergic rhinitis and 22% by eczema [2–4]. These numbers vary a lot between regions, with Northern European countries accounting for the highest prevalence [2]. Food allergies are also common, affecting up to 10% of children [3,5,6]. In a recent population-based cohort of 1,301 European children from UK, France, Greece, Spain, Norway, and Lithuania (2013-2016, mean age: 8 years) [7], we reported similar prevalence for asthma (12%), eczema (21%), and food allergies (10%), but higher prevalence for allergic rhinitis (25%) (manuscript in preparation). Of interest, these symptoms often co-occur in the same subjects (multimorbidity) more often than expected by chance [4].

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

Many early-life lifestyle and environmental factors have been described to contribute to the development of respiratory and allergic diseases such as maternal atopy/asthma, inadequate diet during pregnancy, tobacco smoke, pre-pregnancy obesity, psychological distress, low birth weight, rapid infant growth, or viral respiratory infections [11–13]. Among environmental exposures, exposure to traffic air pollution has been widely studied and it is estimated that 4 million of new paediatric asthma cases are attributable to nitrogen dioxide pollution annually [14,15]. More recently, a growing concern has arisen regarding the impact that environmental chemicals may have on asthma and allergic diseases onset. Among these environmental chemicals, endocrine-disrupting chemicals (EDCs) have gained attention due 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 that are 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 of them are suspected or proven EDCs (e.g. 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 is no common criteria for labelling a chemical as an EDC [21,22]. EDCs include historical persistent organic pollutants (POPs) such as dioxins, polychlorinated biphenyls (PCBs) and pesticides such as dichlorodiphenyltrichloroethane (DDT), which use was banned, as well as emerging persistent and non-persistent compounds such as per- and polyfluoroalkyl substances (PFASs), phenols [e.g. bisphenol A (BPA), parabens], pesticides, and phthalates. These emerging compounds are of most current concern due to their high annual production and potential toxicity.

Human populations are continuously exposed to EDCs through food (e.g. pesticides), food packaging (e.g. phenols, phthalates), cosmetics (e.g. parabens, phthalates), dust inhalation (i.e. phthalates), and consumer goods (e.g. phthalates in paints, PFASs in pans). Human exposure to these chemicals is widespread as observed in many human biomonitoring studies [23–25]. Of concern, exposure to these chemicals is abundant 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 some detoxification pathways and have other sources of exposure such as breastfeeding and crawling. The majority of these compounds can also cross the placental barrier. Although some European countries have started to ban the marketing of certain EDCs such as BPA (e.g. France), new compounds with endocrine-disrupting capacity are continuously being produced, and their potential toxicity is unknown. Indeed, in response to emerging issues related to the growing presence of chemicals in everyday life, the EU 7th Environment Action Programme committed to
the development of a Non-Toxic Environment by 2020 [28], and the current EU Commission has presented the “The European Green Deal” aiming for a non-toxic environment by 2050.

Given their endocrine disrupting activity, exposure to EDCs in vulnerable time periods (i.e. prenatal life) can induce changes in the development of the organs and tissues, with adverse effects occurring in the short- and long-term, such as obesity and metabolic disorders, male and female reproductive disorders, reproductive cancers as well as thyroid disorders, neurodevelopmental delay and IQ loss [21]. Exposure to EDCs has been estimated to cost the European Union $163 billion in total disease and dysfunction across the life-course [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 non-persistent EDCs is inadequate [31]. In this review we summarize the current body of knowledge of the effects of prenatal exposure to non-persistent EDCs, namely phthalates and phenols (bisphenols, parabens, triclosan and benzophenone-3), on asthma and allergic diseases, and the potential biological mechanisms. We also develop recommendations for future studies.

3. Phthalates
Phthalates are a group of phthalic acid diester compounds with straight or branch chain alcohols that are usually 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. The first ones are widely used in polyvinyl chloride (PVC) applications and present in building materials, food containers and many other consumer products. The short-chain ones are further used in non-PVC products including adhesives and personal care products. Phthalates are not chemically bounded to other substances and therefore can be easily released into the air or leached from the plastic, leading to food and environment contamination [33]. Whereas food is considered to be the major source of exposure for the long-chain phthalates, personal care products and indoor air may also be important sources of exposure for short-chain phthalates. In 1999, the EU banned the use of three phthalates [i.e. DEHP, dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP)] in the manufacture of toys and childcare articles. In 2011, these three phthalates and also diisobutyl phthalate (DiBP) were added to the REACH candidate list due to their suspected reproductive toxicity [34].

Mechanisms
Phthalates have been reported to have estrogenic, antiestrogenic and antiandrogenic effects depending on the congener and metabolite analysed. For instance, DEHP seems to have estrogenic activity, whereas monobenzyl phthalate (MBzP), a metabolite of BBzP, seems to have antiestrogenic activity. In any case, further studies are needed to clarify the different activities of the different phthalate compounds [35,36]. Because of this potential endocrine disrupting activity, some phthalates (e.g. DEHP, DiNP, di-isodecyl phthalate (DiDP)) have been reported to bind the peroxisome proliferator-activated receptor γ (PPARγ) [37,38]. In the case of DEHP, it has been observed that this interaction with the PPARγ alters airway cell differentiation and surfactant protein
production in the lungs, which could explain the potential association of DEHP with asthma [39]. The evidence that phthalates increase inflammation responses is not very clear [40]. What seems to be more consistent, according to animal and in vitro studies, is that several phthalates can have adjuvant effects on T helper (Th)2 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 an increased production of the tumour necrosis factor α (TNF-α) by macrophages, and a reduced capacity of migration of such cells [16].

Current evidence from birth cohort studies
The first epidemiological studies in relation to phthalates and respiratory health, exposure assessment was based on measuring home dust phthalates levels or by counting the number of rooms with PVC flooring [42]. Here we revise only studies using biomarkers as exposure assessment to phthalates; a total of thirteen studies have been published so far (Table 1). In 2017, Li et al. performed a meta-analysis including five [43–47] out of these thirteen studies, and observed that prenatal exposure to MBzP was associated with an increased risk of asthma [42]. After this systematic review, eight more studies have been published [48–55]. In two cohorts, in utero exposure to long chain phthalates, 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 being 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 increase in the risk of wheezing and asthma in children; however, the study did not
separately assess the effects of prenatal and postnatal exposures [54]. On the contrary, a decreased risk of wheezing was associated with prenatal exposure to DEP and DnBP metabolites [51]. Regarding allergic disorders, exposure to DiNP and DiBP metabolites was associated with increased risk of eczema [50]. Among sensitized boys, exposure to DiBP and DBP metabolites increased the risk of ever eczema [50]. Food allergies have been assessed in only one cohort; 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, prenatal and postnatal exposures were not differentiated in the models [54]. Finally, two studies explored the link of phthalates with immune biomarkers: one study found an association between a DnBP metabolite and higher Th2 percentage in children younger than 5 years [52], whereas the other one 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 known, produced and used bisphenol is BPA; in 2015, BPA global production was estimated at 5.4 million tonnes [58]. BPA was first described to be an EDC in the late 1930s and has recently been formally identified as an EDC by the European Chemicals Agency (ECHA). Due to concern over neurodevelopment and other toxicological effects, the EU banned BPA in baby bottles in 2011 [59] and its use has recently been restricted in thermal paper [60]. In consequence, 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 to have similar toxicity [61].

Mechanisms
BPA is estrogenic and binds to the two estrogen receptors (ER) ERα and ERβ, with approximately 10-fold higher affinity for ERβ [62]. It also binds to androgen and progesterone receptors, the PPAR, and the aryl hydrocarbon receptor (AhR), 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 classical nuclear ERs [65,66]. It also binds to the thyroid hormone receptor, inhibiting the transcriptional activity stimulated by triiodothyronine (T3) [64]. This endocrine disruption activity is suggested to explain the immunomodulatory properties of BPA observed in animal and in vitro models [63,64,67,68] as well as in general human population [69]. The immune effects observed in relation to BPA exposure include Th1/Th2 cell shifts, reduction of T regulatory (Treg) cells, which are important cells in controlling pro-inflammatory reactions, Th17 alterations (Th17 are involved in the pathogenesis of various autoimmune and inflammatory diseases), reduced innate immunity, stimulation of B cell amount and activity, and increased oxidative stress and expressions of immunity-related genes [63,64,70]. Altered airway cells in rhesus macaques have also been described [71].
Current evidence from birth cohort studies

Up to now, all studies conducted on the effects of exposure to bisphenols during foetal life on asthma and allergic diseases have focused on BPA (Table 1). As far as our knowledge, only one study has assessed the influence of BPS and BPF on asthma and hay fever using data from 3,500 subjects aged 12 years or older participating in the National Health and Nutrition Examination Survey (NHANES) of 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 three studies showing an association between prenatal exposure to BPA and increased risk of childhood wheeze, chest infections, bronchitis, or asthma [74–76] whereas one study reported a decreased risk of wheeze [77]. After this systematic review, five more studies have been published [48,49,51,53,78]. Three of them reported an increase risk of asthma, low respiratory tract infections, or allergic diseases (i.e. itchy rash and eczema) associated with prenatal exposure to BPA [49,51,78], whereas two studies reported no association neither with asthma, aeroallergies, eczema, nor with immune markers such as immunoglobulins, interleukines, or Th1 and Th2 cytokine-producing cells [48,53]. Sex-specific effects have been identified in only two studies with inconsistent results: one study observed a higher risk of allergic diseases among girls [78] whereas another study observed a higher risk of asthma among boys [51].

4.2 Parabens

Parabens are alkyl esters of p-hydroxybenzoic acid with antifungal and antibacterial properties frequently used as preservatives in cosmetic products, toiletries, foods, and
pharmaceuticals. The most common used are methyl-, ethyl-, propyl-, and butyl-paraben, which are used alone or in the form of a mixture to increase their efficacy. Parabens enter in the human body mainly through ingestion or skin absorption, but parabens are also present in dust and indoor air. In the last decades, the production of parabens has experimented a rapid increase. In the early 2000s it is estimated that parabens were present in more than 90% of cosmetic products [79]. Due to their cytotoxicity and endocrine disrupting properties, EU restricted the content of parabens in cosmetic products as preservatives to not exceed a concentration of 0.4% for a single ester and 0.8% for a mixture of parabens [80].

Mechanisms

Given that these compounds are meant to have antimicrobial activity, such activity could be altering microbiota in the gut (or in other body sites) and shift lymphocytes CD4+ response towards Th2, associated with allergy, eczema and other diseases [81]. In fact, a study conducted in 2012 in almost 900 school aged children in the US observed that concentrations of parabens were associated were associated with increased levels of immunoglobulin E (IgE) [82]. However, this kind of information in relation to prenatal exposure is lacking. In addition, parabens of long alkyl chains (e.g. decyl-paraben) induce the release of histamine [16]. For instance, heptyl-paraben, another long alkyl chain paraben used as 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 capacity to supress immune response [83].
Current evidence from birth cohort studies

A total of three cohort studies, all published in 2018, have evaluated the effect of prenatal exposure to parabens and asthma and allergic outcomes in the offspring (Table 1). Two of them observed a decreased risk of asthma [52] and allergic sensitization (in this second study only in girls) [84] associated with exposure to propyl-paraben, and a lower percentage of Th1 and Th2 cells associated with exposure to methyl-paraben [52]. On the contrary, one study, which only included boys, observed increased risk of asthma following exposure to ethyl-paraben [49].

4.3 Triclosan

Triclosan is widely used as antimicrobial agent and preservative in cosmetics, personal care products such as toothpaste, detergents, and other household cleaning products. Ingestion and dermal absorption are the main routes of exposure. Of interest, triclosan chemical structure is similar to PCBs, BPA, dioxins, and thyroid hormones [85]. In 2002, the worldwide production of triclosan exceeded 1,500 tons per year [85]. Although the use of triclosan is not highly regulated, in light of mounting evidence on the potential health effects, some companies have decided to remove triclosan from their products.

Mechanisms

As with parabens, the antimicrobial activity of triclosan might alter human microbiota and shift immune response towards Th2 [81]. A study previously mentioned also showed that IgE levels were increased in a population of school aged children with increasing exposure to triclosan [82]. But, as commented above, this kind of
information in relation to prenatal exposure is lacking. In addition, it has been observed that triclosan can inhibit natural-killer cells (NK) lytic function 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) [16].

**Current evidence from birth cohort studies**

Five cohort studies have assessed so far whether foetal exposure to triclosan increases the risk of asthma and allergies development in childhood (Table 1). Four of them 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 observed a decreased risk of asthma and wheeze, but in girls only [84].

**4.4 Benzophenone-3**

Benzophenone-3 or oxybenzone is a phenolic compound frequently used as ultraviolet filter in sunscreen and personal care products as fragrance enhancer. Benzophenone-3 is one of the most widely used benzophenone for UV filters. There are other benzophenones, such as 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. BP-3 is lipophilic and can bioaccumulate 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, EU regulated the use of benzophenone-3 as a UV filter up to 6% in cosmetic sunscreen products and up to 0.5% in all types of cosmetic products [88].
Mechanisms

There is very limited information on the potential mechanisms by which benzophenone-3 may increase the risk of allergic diseases and asthma. Similarly to the previous compounds analyzed, a recent review suggests that it could stimulate the differentiation of T cells towards Th2 [16]. However, further animal and in vitro studies are needed to better understand the potential mechanisms.

Current evidence from birth cohort studies

Only two studies evaluated the potential effects of benzophenone-3 on asthma and allergic diseases in childhood (Table 1). One of them showed a lower risk of wheezing among girls [51] whereas the other one did not observe any association [52].

5. Summary of the state of the evidence and future research

In this review we describe the current body of evidence of the effects of exposure during pregnancy to phthalates and phenols on the development of asthma and allergic diseases in childhood. Although the number of studies on phthalates and BPA is quite extensive, there are still inconsistencies across them. For triclosan, parabens, and benzophenone-3 the number of studies is very limited. This insufficient evidence has resulted in the potential effects of EDCs on immune and respiratory health not being considered when estimating their burden [29]. Indeed, their burden is calculated only considering the effects on obesity, diabetes, reproductive problems, IQ loss and behavioural problems [29]. Of relevance, although the EU recently funded twelve
projects to improve identification of EDCs [89] (call SC1-BHC-27-2018), none of them consider the effects on respiratory or immune health for their identification. Due to the scarcity of studies and their inconsistent results, further work is needed to elucidate their role on asthma and allergies.

Discrepancies across studies may reflect differences in chemicals use between countries and/or sociodemographic characteristics of the populations. The sample size of the majority of studies is limited (less than 600), which may hinder the identification of most vulnerable subgroups (e.g. according to sex, sociodemographic characteristics, preterm births). Inconsistencies among studies may also be due to the non-monotonic dose-response curves associated with exposure to EDCs (i.e. low doses can have more potent effects than higher doses) [90]. Combining data from different birth cohorts can lead to more conclusive results, and also to an appropriate analysis including effect modifiers and an adequate modelling of exposure-response relationship [91,92]. In the majority of cohorts, pregnant women were recruited more than a decade ago (Table 1) and new EDCs could not be detected at that time. In the INMA cohort for example, where pregnant women were recruited between 2004 and 2006, BPS was not detected in most of the maternal urine samples (unpublished results). Although the new substitutes have similar structure and mechanisms of action than the initial ones, and hence we 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 revised the literature regarding exposure to currently used pesticides (e.g. organophosphate pesticides), glycol ethers, or polycyclic aromatic
hydrocarbons (PAHs), which can also have endocrine disrupting activity, and hence affect the development of asthma and allergies.

5.1 Improving exposure assessment

Because we expect small effect sizes associated with exposure to EDCs, a reliable exposure assessment is needed to assess the effects of these compounds on respiratory and immune health. All cohort studies, but two, determined the levels of phthalates and phenols in spot urines samples collected during pregnancy (Table 1). Two cohorts [46,84] used maternal serum or plasma to assess exposure to these non-persistent EDCs. After ingestion, phthalates and phenols are rapidly metabolized and excreted in urine in few hours or days. A low proportion is retained in blood and circulating levels are usually lower than urinary levels; hence, urinary measurements are most preferred [93]. However, due to their fast excretion, urinary concentrations determined in a spot urine sample only reflect exposure during a short period of time. Substantial measurement error, as the one that occurs when using a limited number of urines to characterize long-term/chronic exposure, can result in attenuated associations in analyses linking an exposure with a health outcome if the error of exposure assessment is random and consequently not associated with the outcome (non-differential) [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 amount to 80% [95]. Recently, new sampling strategies have been postulated to limit exposure misclassification by pooling many urine samples per subject [95,96]. This pooling approach is feasible in terms of logistics and does not increase the analytical costs since only one urinary pool is finally analysed [96]. We have 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 to (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 chronic exposure. Another alternative, is the use of personal silicone wristbands as personal passive samplers [98], which also provide information on long-term exposure and have good correlation with metabolites in urine for some compounds such as PAHs [99].

5.2 Improving assessment of asthma and allergic phenotypes

A proper characterization of the asthma and allergy phenotypes is required to adequately identify the underlying environmental causes. Almost all cohorts collected information on asthma and allergic symptoms using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire administered to the mothers (Table 1). The use of standardized questions allows comparability of results across studies but they can be subject to an 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 some studies did [44,45], or by performing physician examination of those children with respiratory symptoms as done by the Columbia Center for Children's Environmental Health Cohort (CCCEH) [77], although we recognize this is not always possible. Allergy diagnosis can be better characterized by performing the skin prick test, the fraction exhaled nitric oxide measurement test (FeNO), or by measuring IgE levels, as performed by some cohorts (Table 1). Due to the heterogeneity of asthma and allergic...
phenotypes, there is no uniform set of diagnostic criteria and their definition can vary among studies. In the CCCEH cohort, for example, allergist or paediatric pulmonologists defined asthma considering current asthma-related symptoms and medication, postbronchodilator test, and history of asthma on previous questionnaires [77], whereas in INMA we defined asthma following the MeDALL recommendations [100] considering questions on doctor-diagnosis, asthma treatment, and wheezing symptoms [45]. In spite of that, we should also consider that although doctor diagnosis provides more reliable information than parental reported respiratory symptoms, variations in asthma and allergic diseases prevalence between countries may reflect different diagnostic criterion - readily diagnosed in some countries while unrecognised in others [58]. Future studies assessing the effects of prenatal exposure to EDCs on asthma and allergy should include a better characterization of the asthma and allergic phenotypes by considering alternative tests and respiratory symptoms trajectories [101], assessing food allergy (since only one study has assessed it), and following-up children at later ages (in all studies children were younger than 11 years) to elucidate whether the effects of early-life exposure to EDCs persist into adolescence and adulthood. Moreover, we encourage to consider multimorbidity, 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 related with EDCs [21], such as other respiratory problems (e.g. lower lung function) [102], cardiovascular and metabolic diseases [103], and some mental health disorders [e.g. attention deficit hyperactivity disorder (ADHD)] [104].

5.3 Assessing mixtures of EDCs
Humans are exposed to multiple EDCs at the same time and it is important to understand how these multiple compounds interact and which are the EDCs of most toxicological concern in relation to asthma and allergic outcomes. The majority of studies included in this review assessed a single EDC at a time. Some of the studies adjusted the models for another EDC (e.g. [44,45]) while Smit et al. [46] considered many EDCs at the same time (phthalates, perfluoroalkyl compounds, DDT metabolites, and PCBs). To deal with the high correlation among these chemicals, they applied a dimension reduction method called principal components analysis (PCA), which transforms 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 shown that mixtures often have higher toxicity than the individual compounds [106,108]. Whyatt et al. [109], for example, using data from the CCCEH cohort, tested the interaction between maternal phthalates 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 taking into account the potential for co-pollutant interaction and confounding between exposures, and a careful consideration of the biological mechanisms and modes of action involved [17,106,110]. New statistical tools to estimate the effect of multi-pollutant mixtures are being developed, particularly within the framework of the 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 for considering mixtures in chemical risk assessment and regulation [108,112].

5.4 Exploring the biological mechanisms

Understanding the biological pathways through which EDCs can increase the risk of asthma and allergies development is key to establish causal inference. Up to know, studies have shown 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 (e.g. alterations of DNA methylation) [113,114]. However, epigenetic studies require large sample sizes 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, including 39 studies with DNA methylation data, offers a great opportunity to address this issue [115]. Another potential mechanism just starting to be studied is through changes on gut microbiota; the gut microbiome and the immune system develop in parallel and with a strong cross-talk throughout life. Some EDCs have been described to enhance gut dysbiosis in animal models, linked with immune alterations [116–118]. It is of particular interest to study the effect of those compounds specifically designed to have an antimicrobial action (e.g. triclosan and parabens) [81].

Conclusion

EDCs exposure during vulnerable periods can disrupt the development and functioning of the immune and respiratory system and increase the risk of asthma and allergic diseases in children. In this review we summarized the current evidence of the effects of
prenatal exposure to phthalates and phenols on respiratory outcomes and allergies concluded that the evidence is still insufficient. Studies with a thoughtful exposure assessment design, a good characterization of the asthma and allergic phenotypes, and which consider potential biological mechanisms and EDCs mixtures, are needed to better understand the burden of EDCs on the respiratory and immune system. This research will contribute to implement public health policies to reduce EDCs exposure in the community, particularly in pregnant women. Current EU regulations on the registration, evaluation, authorisation and restriction of chemicals, additive regulation, and cosmetics regulation do not cover EDCs efficiently [21]. Given the widespread exposure of EDCs and their potential toxicity, the application of the precautionary principle (i.e. act avoiding potential harmful issues without complete scientific certainty) would be the best approach, particularly to protect the most vulnerable groups such as pregnant women and children. EU chemical legislation, which is currently dominated by substance-by-substance approach, should move towards avoiding entire chemical classes (i.e. hazard specific regulations) instead of individual compounds.

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Table 1. Studies on prenatal exposure to non-persistent EDCs and asthma and allergic diseases (ordered by year and author)

| Author (Year) | Country (cohort name) | Years of recruitment | N | Child age | Exposure assessment | Outcomes assessment | Statistically significant main findings |
|---------------|-----------------------|----------------------|---|------------|---------------------|----------------------|----------------------------------------|
|               |                       |                      |   |            |                     |                      |                                        |
| Phthalates    |                       |                      |   |            |                     |                      |                                        |
| Just et al (2012) [43] | US (CCCEH)            | 1999-2006            | 407 | 3-60 m    | 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 metab ↑ 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 metab ↑ 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] | US (CHAMACOS)         | 1999-2000            | 392 | 2-7 y     | 2 urines            | ISAAC, Th1/Th2 cells | asthma, eczema, aeroallergies DnBP metab ↑ Th2 |
| 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 metab ↓ 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 metab ↑ eczema DBP and DiBP metab ↑ 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 metab ↑ wheeze b DiNP metab ↑ |
| Study                                      | Country/Study | Time Period | Sample Size | Sample Group | Exposure | Outcome |
|-------------------------------------------|---------------|-------------|-------------|--------------|----------|---------|
| Berger et al (2019) [53]                  | US (CHAMACOS) | 1999-2000   | 392         | 2-7 y        | 2 urines | ISAAC, Th1/Th2 cells asthma, eczema, aeroallergies bronchiolitis/bronchitis b |
| 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 metabol ↑ food allergy, ↓ atopic dermatitis MBzP, DEHP metabol ↑ wheeze, asthma |
| Berger et al (2019) [53]                  | US (CHAMACOS) | 1999-2000   | 392         | 2-7 y        | 2 urines | ISAAC, Th1/Th2 cells asthma, eczema, aeroallergies |
| 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 metabol ↑ food allergy, ↓ atopic dermatitis MBzP, DEHP metabol ↑ wheeze, 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 metabol ↑ food allergy, ↓ atopic dermatitis MBzP, DEHP metabol ↑ wheeze, 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 metabol ↑ food allergy, ↓ atopic dermatitis MBzP, DEHP metabol ↑ wheeze, asthma |
| 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, IgEs 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 m          | 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 ↑ bronchiolitis/bronchitis, asthma |
| Berger et al (2019) [53]                  | US (CHAMACOS) | 1999-2000   | 392         | 2-7 y        | 2 urines | ISAAC, Th1/Th2 cells asthma, eczema, aeroallergies - |
| Parabens                                  |               |             |             |              |          |         |
| Berger et al (2018) [52]                  | US (CHAMACOS) | 1999-2000   | 392         | 2, 5, 7 y    | 2 urines | ISAAC, Th1/Th2 cells asthma, eczema, aeroallergies propyl-paraben ↓ asthma Methyl-paraben ↓ Th1, Th2 |
| Vernet et al (2018) [49]                  | France (EDEN – only boys) | 2003-2006 | 587         | 5 y          | 2 urines | ISAAC bronchiolitis/bronchitis, wheeze, asthma ethyl-paraben ↑ asthma |
| Study                        | Region/Country | Duration | Age | Sample Type | Methods | Outcomes | Results |
|-----------------------------|----------------|----------|-----|-------------|---------|----------|---------|
| Lee-Sarwar et al (2018) [84] | US (VDAART randomized clinical trial) | 2009-2011 | 3 y | 2 pooled plasma samples | Questionnaires, IgE | wheeze, asthma, allergic sensitization | propyl-paraben ↓ allergic sensitization (only girls) |
| Ashley-Martin et al (2016) [86] | Canada (MIREC) | 2008-2011 | birth | 1 urine | IgE, IL-33, thymic stromal lymphopoietin cells | - | - |
| Berger et al (2018) [52] | US (CHAMACOS) | 1999-2000 | 2, 5, 7 y | 2 urines | ISAAC, Th1/Th2 cells | asthma, eczema, aeroallergies | - |
| Buckley et al (2018) [51] | US (Mount Sinai Children's Environmental Health Study) | 1998-2002 | 6-7 y | 1 urine | ISAAC | wheeze, asthma, atopy | - |
| Lee-Sarwar et al (2018) [84] | US (VDAART randomized clinical trial) | 2009-2011 | 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 | 5 y | 2 urines | ISAAC | bronchiolitis/bronchitis, wheeze, asthma | - |
| Buckley et al (2018) [51] | US (Mount Sinai Children's Environmental Health Study) | 1998-2002 | 6-7 y | 1 urine | ISAAC | wheeze, asthma, atopy ↓ wheeze (only girls) |
| Berger et al (2018) [52] | US (CHAMACOS) | 1999-2000 | 2, 5, 7 y | 2 urines | ISAAC, Th1/Th2 cells | asthma, eczema, aeroallergies | - |

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 = diisobutyl phthalate; DiDP = di-isodecyl phthalate; DiNP = diisononyl phthalate; DnBP = di-n-butyl phthalate; EDEN = Etude des Déterminants pré et postnataux 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

*At the time of outcome assessment (m = months; y = years).

**All results were borderline statistically significant.

*Phthalate metabolites are different among studies.

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