Early-Life Environmental Influences on Allergic Diseases

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1 Introduction

An allergy is a chronic condition involving an abnormal reaction to an ordinarily harmless substance (i.e., an allergen). The resultant response can lead to conditions such as asthma, food allergies, atopic dermatitis (eczema), allergic rhinitis or hay fever, and anaphylaxis. Allergens can include aeroallergens such as dust mites, mold, and plants pollen, as well as food allergens such as milk, eggs, wheat, nuts, or fish proteins. Responses to allergens result in allergic symptoms, including increased levels of immunoglobulin-E (IgE). Allergies first present in early childhood. Interestingly, the severity of symptoms of allergic asthma in childhood predicts disease persistence into adulthood. Type 2 immune responses are the basis of an allergic response. However, increasing allergies in early childhood cannot be simply explained by type 2 immune responses only. It is clear that the genetic component certainly contributes to allergy susceptibility. In fact, various gene variants associated with Th2 cell differentiation are noted as risk factors for allergy [15]. For example, loss-of-function mutation(s) in the *filaggrin* gene is a risk factor of atopic dermatitis. However, *filaggrin* gene mutations can explain only 40% of the cases of atopic dermatitis [67], and the remaining 60% are thought to occur due to environmental risk factors. Furthermore, epigenetic modifications play a key role in the differentiation of allergy-related T-cell lineages as well as influence the balance between distinct Th cell populations such as Th1, Th2, and regulatory T cells. Epigenetic regulation also mediates the effect of various environmental exposures resulting in both allergy protection and conferring susceptibility to allergic diseases [65]. Many environmental factors have been identified and investigated as "environmental influences of allergic diseases." These include various toxic and harmful

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physical, chemical, biological, and sociopsychological factors. Such factors are introduced into people's lives through their environment (e.g., via air), water source, soil, indoor public spaces, food, etc. In regard to chemical factors, the prevalence of asthma has increased since the 1970s, which coincides with an increased use of numerous new chemicals in manufacturing processes, with increased exposure of the general population during the same period. Asthma and allergy have not only a genetic but also an environmental component, and, because of the increases in incidence, prevalence cannot be due solely to genetics. These newly produced synthetic chemicals have shown endocrine-disrupting effects on humans, which interfere in some way with hormone action and can alter endocrine function such as immune, reproductive, endocrine, cardiopulmonary, and brain systems [84]. In this section, we provide up-to-date evidence based on epidemiological findings, specifically focused on the influence of prenatal and postnatal environmental chemical exposures, such as persistent organic pollutants (POPs) and short half-life compounds, on early childhood allergic diseases outcomes. We also investigate the possible pathophysiological mechanisms involved based on experimental data.

2 Persistent Organic Pollutants (POPs)

2.1 Perfluoroalkyl Substances (PFAS)

Perfluoroalkyl substances (PFAS) are persistent bioaccumulative chemicals which are widely used in industry including textiles, non-stick housewares, food packaging, furnishings, fire-fighting formulations, and more. The main exposure routes of PFAS for people are through the intake of contaminated food and water [28], although inhalation and ingestion of indoor dust are also contributing factors [40]. Since perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) were included in the Stockholm Convention on Persistent Organic Pollutants, both substances have been replaced by shorter or longer carbon-chain PFAS. In human biomonitoring, results have shown that the exposure levels of PFOS and PFOA have decreased in recent years, while the levels of shorter and longer carbon-chain have increased [31, 61, 78]. Despite the introduction of the shorter or longer carbon-chain PFAS, epidemiological studies have reported that these substances are immunotoxic and immunomodulating (Table 1). Data from a birth cohort from the "Hokkaido Study" showed that prenatal exposure to PFOS was linked to decreased cord blood IgE levels among female infants [63] and reduced risk of eczema among 2-year-old girls [62]. In the same population, prenatal exposure to longer chain PFAS, such as perfluorohexane sulfonate (PFHxS), perfluorododecanoic acid (PFDoDA), and perfluorotridecanoic acid (PFTrDA), was linked to reduced risk of eczema at 4 years old [34]. Similar results have been reported from other birth cohorts. The Norwegian Mother and Child (MoBA) cohort has reported that prenatal exposure to longer carbon-chain PFAS and perfluoroundecanoic acid (PFUnDA) was inversely linked to a risk of atopic eczema [44]. Furthermore, a study conducted

Table 1 Early-life exposure to PFAS and associations with allergies or infectious disease

Author, year	No. of participants and age	Exposure	Outcome	Results
Stain et al. (2016) USA	1191 (12–19 years)	PFOS, PFOA, PFHxS, PFNA in maternal blood	Measles, mumps, rubella	PFOS was associated with decrease in rubella and mumps antibody. No adverse association between exposure and current allergies
			Asthma, wheeze, rhinitis, allergy	
Granum et al. (2013) Norway	640 (3 years)	PFOS, PFOA, PFHxS, PFNA in maternal blood	Vaccine antibody levels, common infectious diseases, and allergy- and asthma-related health outcomes	Inverse association between the level of anti-rubella antibodies at 3 years and PFAS. A positive association between the maternal PFOA and PFNA levels and the number of episodes of common cold. No associations were found between maternal PFAS and the allergy- and asthma-related health outcomes
Smit et al. (2015) Greenland and Ukraine	1024 (5–9 years)	PFHxS, PFHpA, PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFDoDA in maternal blood	Wheeze, rhino-conjunctivitis, eczema (ISAAC)	PFAS in maternal blood was inversely associated with wheeze
Impinen et al. (2019) Norway	1270 (3 years), 972 (7 years)	PFOS, PFOA, PFHxS, PFNA, PFUnDA, and PFHpS in maternal blood	Asthma	Prenatal exposure to lPFAS and PFUnDA was inversely associated with risk of atopic eczema. Significant positive associations were seen between PFASs and airway infections
			Atopic eczema	
			Food allergy, infectious diseases	
Okada et al. (2012) Japan	343 (at birth)	PFOS, PFOA in maternal blood	Cord blood IgE	Prenatal exposure to PFOS was associated with decreased cord blood IgE levels among girl infants, but not associated with any allergic symptoms at 1.5 years of age

(continued)

Table 1 (continued)

Author, year	No. of participants and age	Exposure	Outcome	Results
Okada et al. (2014) Japan	2063 (2 years)	PFHxS, PFHxA, PFHpA, PFOS, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA in maternal blood	Wheeze, rhino-conjunctivitis, eczema (ISAAC)	Prenatal exposure to PFOS was associated with reduced risk of eczema among girls at 2 years of age
Goudarzi et al. (2016) Japan	1558 (4 years)			Prenatal exposure to PFHxS, PFDoDA, and PFTrDA was associated with reduced risk of eczema
Goudarzi et al. (2017) Japan			Otitis media, pneumonia, RS virus, varicella, total infectious diseases	Prenatal exposure to PFHxS, PFDoDA, and PFTrDA was associated with increased risk of infectious diseases
Dalsager et al. (2016) Denmark	346 (1–4 years)	PFOS, PFOA, PFHxS, PFNA, PFDA in maternal blood	Fever, stuffed or runny nose, cough, diarrhea, and vomiting	Prenatal exposure to PFOS and PFOA and the prevalence of fever at 1–4 years of age
Grandjean et al. (2012) Denmark	587 (5 years, 7 years)	PFOS, PFOA in maternal blood	Tetanus and diphtheria antibody	A twofold increase levels of PFAS was associated with a decline in the diphtheria antibody levels
Zeng et al. (2019) China	201 (3 months old)	PFOA, PFOS, PFDA PFDoDA PFHxS PFNA PFUnDA in maternal blood	Hand-foot-mouth disease antibody	Cord blood PFAS in 3 month-old-infants was associated with significant increase in the risk of hand-foot-mouth disease antibody concentration below clinical protection level

in Greenland and Ukraine showed that a principal component of PFAS in maternal blood, dominated by PFOS, was inversely linked to wheeze at 5–9 years old [68]. On the other hand, some studies are incongruent with those results. A study from Taiwanese asthmatic case-control study reported that positive dose-response associations were found between PFAS concentrations and risk of asthma at 15 years old [25]. National Health and Nutrition Examination Survey, a cross-sectional study, reported that the levels of PFOS were linked to higher odds of diagnosed asthma at 12–15 years old [43].

Data from the same population as Goudarzi et al. showed that prenatal exposure to PFHxS, PFDoDA, and PFTrDA was linked to an increasing risk of infectious diseases at 4 years old [33]. The Denmark Odense Child Cohort has reported that exposure to PFOS and PFOA during the prenatal period increases the prevalence of fever at 1–4 years of age [22]. This inverse association of allergic symptoms and infectious diseases is thought to be plausible due to the immunosuppressive effects of PFAS. Grandjean et al. first reported the possibilities of the immunosuppressive effects of PFAS when they showed that a twofold increase in PFAS levels was linked to a decline in diphtheria antibody levels [35]. Similar associations have been found between prenatal or postnatal exposure to PFAS and childhood vaccination antibodies, such as mumps and rubella [36, 71]. Moreover, the Guangzhou Birth Cohort Study has reported that cord blood PFAS was linked to a significant increase in the risk of hand-food-mouth-disease antibody concentration below the level of clinical protection among 3-month-old infants [86]. These findings are in line with animal studies. It has been demonstrated that in PFOS-exposed mice, IgM, which was suppressed, responses to T-cell-dependent and T-cell-independent antigens and natural killer (NK)-cell function [24, 37]. However, the experimental conditions employed used higher doses than the general exposure levels seen in humans. Evidence from experimental studies cannot be directly related to human health outcomes. Moreover, epidemiological findings are not fully consistent; this may be due to study designs, the age to which the health outcomes are related, confounding factors, and varied definitions of outcomes. Evidence regarding the immunosuppressive effects of PFAS, especially longer carbon-chain of PFAS in early childhood, is still under consideration.

2.2 PCBs/PCDDs/PCDFs

Polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins, and polychlorinated dibezofurans (PCDDs/PCDFs) have a long half-life and are categorized as POPs. PCBs, PCDDs, and PCDFs exist persistently not only in the food chain but also in the environment. Primary sources of exposure to these compounds are food items such as fish, seafood, meat, and eggs. PCBs, PCDDs. For many years, it has been shown that PCDFs accumulate mainly in adipose tissue due to the high lipophilicity and resistance to biodegradation. In bodies, they traverse the placenta and are transferred to fetal tissues and cord blood. The most toxic congener of

Table 2 Prenatal exposure to PCBs and dioxins at high levels and association with allergies or infectious diseases

Authors (year), place	No. of participants and age	Exposure	Results
Dallaire et al. (2004[a], 2006[b]) Nunavik in Canada	a: 199 (1 years)	PCB 153 in cord blood	a: GI infections/PCB: RR = 1.7 (1.0–2.8), otitis media/PCB: RR = 1.6 (1.0–2.5)
	b: 343 (5–7 years)		b: Acute otitis/PCB: RR=1.1 (1.1-1.1), lower respiratory infections/PCB: RR = 1.1 (1.0–1.2)
Heilmann et al. (2006) Faroe Island	a: 129 (7 years)	PCBs in maternal serum	a: Decreased antibody response to diphtheria toxoid/PCB:24% (p = 0.04)
	b: 119 (18mo.)		b: Decreased antibody response to tetanus toxoid/PCB: 17% (p = 0.03)
Park et al. (2008)	982 (3–4 days)	PCBs in maternal serum	Small thymus size/PCBs: β = −36(p = 0.047)
Yu et al. 1998 Taiwan	105Yuchengs / 101Controls (born between 1978 and 1987)	PCBs/PCDFs by maternal infestation of contaminated rice oil	Bronchitis/PCDFs (6 months)
			Respiratory tract infections/ PCDFs (6 years)
			Ear infection/PCDFs (6 years) (significant higher frequency in Yuchengs than unexposed controls)

PCDDs/PCDFs is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The offspring of maternal rats treated with TCDD during pregnancy are more sensitive to immune toxicity caused by TCDD compared to adult rats and the negative influence that occurs at crucial windows of maturation persists later in life. Besides, the aforementioned toxic susceptibility appears to be sex-dependent. The offspring of male rats is more sensitive to TCDD-mediated inhibition of T cell activity than that of female rats [83].

There have been reports of exposure of high levels of PCBs/PCDDs/PCDFs, accidental poisoning, or contaminated food intake of PCBs/PCDDs/PCDFs in humans (Table 2). In one such incident in Taiwan Yucheng, pregnant women were exposed to high levels of PCDFs, and their children were more frequent to have bronchitis and reduced serum levels of immunoglobulins at 6 months of age and more likely to develop diseases of influenza and otitis media at 6 years of age. In Japan, pregnant women exposed to contaminated food were exposed to high levels of PCB. The children that these women bore were more likely to catch colds and gastrointestinal symptoms [30]. In Inuit infants born to mothers who were exposed to contaminated marine mammals, higher levels of prenatal PCB caused an apparent increased incidence of infections (e.g., acute otitis) and respiratory problems [20, 21]. On the Faroe Islands, PCB levels in maternal serum were inversely linked

Table 3 Prenatal exposure to PCBs and dioxins at environmental levels and association with allergies or infectious diseases

Authors (year), Place	No. of participants and age	Exposure	Results
Weisglas-Kupherus et al. (2000) Rotterdam in Netherland	193 mother-infant pairs (42 months)	PCBs (118, 128, 153, 18) Dioxins (PCDD, PCDF, Mono-ortho PCB) in maternal blood and breast milk	Asthma/∑PCB (maternal blood): (OR: 0.44; 95 % CI: 0.18–0.99)
			Otitis media/mono-ortho PCB TEQ (breast milk): (OR: 1.2; 95% CI: 1.0–1.3)
			Cough
			Chest congestion
			Phlegm/dioxin TEQ (breast milk): (OR: 1.1; 95% CI: 1.0–1.1)
Sunyer et al. (2005) Menorca in Spain	482 mother-infant pairs (4 years)	PCBs (28,52,101,118,153,138,180) in cord blood	Asthma/PCBs: No association
ten Tusscher et al. (2003) Amsterdam in Netherland	27 mother–infant pairs (8 years)	17 PCDDs /PCDFs in breast milk	Allergies/dioxins: Slope = −0.14 ($p = 0.023$)
			Infections/dioxins: No association
Miyashita et al. (2011) Hokkaido in Japan	364 mother-infant pairs (1.5 years)	Dioxin-like PCBs, PCDDs, PCDFs in maternal blood	Otitis media (male)/ PCDFs (OR: 2.5, 95% CI: 1.1–5.9)
			Otitis media (male)/ 2,3,4,7,8-pentachlorodibenzo-furan (OR: 5.3; 95% CI: 1.5–19)
Hansen et al. (2014[a], 2016[b]) [38, 39] Aarhus in Denmark	421 mother-infant pairs (20 years)	PCBs, PCDDs, PCDFs in maternal blood	a: Asthma medical intake/ PCB118 (OR: 1.90; 95% CI: 1.12–3.23)
			b: Allergic sensitization/ PCBs, PCDDs, PCDFs: No association
			c: Airway obstruction/ PCBs (OR: 2.96; 95% CI: 1.14–7.70)
Miyashita et al. (2018) Hokkaido in Japan	264 mother-infant pairs (7 years)	Dioxin-like PCBs, PCDDs, PCDFs in maternal blood	Wheezing/PCBs, PCDDs, PCDFs (OR: 7.8; 95% CI: 1.4–42.9)

to an antibody response to diphtheria toxoid in 18-month-old children and tetanus toxoid in 7-year-old children [41]. According to a study in Eastern Slovakia, higher PCB levels in maternal serum were linked to newborns with a smaller thymus, the organ associated with lymphocyte maturation [64].

The associations between prenatal exposure to PCBs and dioxins at environmental levels and allergies or infectious diseases among general population have been

also reported (Table 3). In the Rotterdam study, children's otitis media and chicken pox were more prevalent due to maternal exposure to PCBs during pregnancy. Moreover, these implications were associated with a decrease in measles, mumps, and rubella reactivity after primary vaccination and a growing number of T lymphocytes in 42-month-old children [79, 80]. In contrast, in the Amsterdam study, children's allergies were found to have decreased at 8 years of age due to increased maternal dioxin levels [73]. PCB levels in cord blood have no associations with the prevalence of asthma in 4-year-old children in Spain [72]. In Japan, PCBs/PCDDs/PCDF levels in breast milk were notably linked to an increase of lymphocyte subset ratio in the peripheral blood of breast-fed infants at 10 months of age [60]; however, there was no observation in another cohort of Japanese infants at 12 months of age [47]. A systematic review published by Gascon et al. included several studies demonstrating a higher risk of respiratory infections, including acute otitis media, among infants [16, 20, 32, 58] with regard to in utero exposure to PCBs and/or dioxins. The majority of the current knowledge surrounding in utero exposure to PCBs/PCDDs/PCDFs in the context of downregulation of immune response and higher incidences of infectious symptoms in early infancy has been relatively consistent.

Regarding long-term effects, in a Danish cohort, the number of children with asthma was higher during a follow-up period lasting for 20 years according to higher maternal PCBs during pregnancy. Airway obstruction in children but not allergic sensitization, at age 20, was associated with maternal PCB levels during pregnancy in that cohort [39]. The Hokkaido Study in Japan reported that exposure to PCBs/PCDDs/PCDFs in utero may modify immune responses in offspring, resulting in a growing risk of allergy among school-age children. Besides, male infants may be more susceptible to maternal exposure to PCBs/PCDDs/PCDFs [57]. In summary, excluding accidental poisoning and contaminated food intake, the general population is continually exposed to PCBs/PCDDs/PCDF at relatively low levels. Even at low-level exposure, prenatal PCB/PCDD/PCDF exposure may modify the immune responses of the offspring of exposed individuals, resulting in an increased risk of allergy and infection during childhood and adolescence. There is insufficient evidence detailing the long-term effects of exposure to PCBs/PCDDs/PCDFs. Therefore, further studies targeted at the general population are vital to elucidate the long-term influence of such exposure.

2.3 Brominated Flame Retardants (BFRs)

Brominated flame retardants (BFRs) consist of different groups of chemicals with a range of physiochemical properties. BFRs are widely used in industrial applications such as production of polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), tetrabromobisphenol A (TBBPA), as well as other brominated compounds. PBDEs contain up to 10 bromine atoms attached to 2 aromatic rings, which results in 209 different congeners which are structurally similar to PCBs. Exposure to BFRs from indoor environments is of particular

concern because of their widespread use within household interiors, building materials, electrical appliances, as well as rubber products. More specifically, house dust is thought to be a significant means of exposure to PBDEs for toddlers, children, teenagers, and adults, accounting for more than 50% of the total PBDE intake [45]. Widespread contamination of PBDEs in the environment and their detection in people and wildlife have raised concerns regarding adverse health effects [55]. Several reviews have suggested that BFRs, especially PBDEs, have potentially adverse effects on endocrine functions, the central nervous system, and reproductive systems in experimental studies [19, 54]. PBDEs and HBCDD have been listed as POPs in the Stockholm Convention because of their potentially negative influence on human health, their persistence in the environment, as well as bioaccumulation potential. In epidemiological studies, adverse effects on neurodevelopment [77], birth outcomes [17], changes in the levels of thyroid hormones [18, 77], and reproductive hormone levels [27] have been reported. As for immunological effects, however, experimental and epidemiological data is lacking. An in vitro study suggested that BFRs can induce or enhance immune or allergic responses by increasing antigen presentation-related molecule expression and IL-4 production [49]. A case-control study reported that, serum levels of BDE-209, which is the most widely used PBDE in China and was dominantly detected in the study population, was linked to an increased risk of asthma among children. However, levels of BDE-209 or other PBDEs in house dust were not associated with any allergic symptoms [14, 56].

3 Short Half-Lived Chemicals

3.1 Phthalates

Phthalates are plastic additives (plasticizers), which are added to plastics and perfumes and are widely contained in consumer products and personal care products (PCPs). Phthalates are nonpersistent, not bioaccumulative, and therefore short half-life compounds which are excreted in urine within hours to 2 days. Due to their endocrine-disrupting effects, some phthalates, such as di-2-ethylhexyl phthalate (DEHP) and di-n-butyl phthalate (DnBP), have been partly regulated for their use in food containers for fatty foods, as well as in children's toys and mouthing products. However, their use in other consumer products such as PCPs, furniture, and indoor materials is not regulated. We are exposed to phthalates from various consumer products on a daily basis. It is, therefore, important to investigate the possible associations between exposure to phthalates and allergic diseases. This is especially critical since the hand-to-mouth behavior of infants and toddlers is thought to be the main exposure route of phthalate exposure among young children. Moreover, phthalates are known to have adjuvant effects on allergies, which are consistent with experimental studies [48, 53]. In experimental studies, adjuvants induced production and differentiation of Th2 cells in mice, which in turn promoted

IgE and IgG1 production. In a human experimental study, healthy human participants showed no inflammatory responses to short-term inhalation of house dust which contains DEHP. Nevertheless, nasal exposure to dust mite in allergic participants showed elevated IL-5, IL-6, granulocyte-colony stimulating factor, and eosinophil cationic protein levels even after short-term exposure to low DEHP doses [23].

Epidemiological studies are mainly designed to use the levels of phthalate metabolites in urine or of phthalates in house dust as exposure assessments (Table 4). In human biological samples, both prenatal and postnatal exposure levels are considered; however, in dust samples, only postnatal time periods are investigated. Currently, evidence regarding the relations between prenatal exposure to phthalates in house dust and allergies in early childhood is lacking. Data generated using phthalates in house dust as a proxy for postnatal exposure assessment shows quite accordant results, in which higher house dust levels of butyl benzyl phthalate (BBzP), DEHP, and DnBP were linked to an increase in the risk for allergies among school-age children [1, 6, 8, 42, 51]. Some of these studies investigated the relations with urinary phthalate metabolite levels; however, no associations were found between urinary phthalate metabolites and allergies. In prenatal exposure, metabolites of diisononyl phthalate (DiNP) were associated with an increase in the risk for childhood asthma [7]. In this study, two spot urine samples were collected from pregnant women during the first and second trimester of pregnancy. Additionally, the prenatal exposure to diisodecyl phthalate (DiDP) was linked to wheeze at 5 years old [76]. Data seems to suggest that high molecular weight phthalates, such as DiNP and DIDP which are used as replacements for DEHP, are associated with asthma and respiratory symptoms. However, evidence for the effects of postnatal exposure to phthalates on childhood allergies is still very limited. Since phthalates are nonpersistent and short half-life compounds, the inconsistency of postnatal exposure to phthalates may be due to this and compounded by the fact that only one spot urine collection was used for assessing the effects of phthalate exposure. Intra- and inter-day variances of phthalate metabolites have been reported, and urine sampling in several time points is recommended. Therefore, only one spot urine collection is one of the limitations of exposure assessment of phthalates. On the other hand, levels of phthalates in house dust might not change dramatically on a daily basis, as well as intra-day basis. It is also quite challenging to collect urine samples from children at several time points. Nonetheless, further studies are needed to challenge this and to allow for robust analysis of postnatal phthalate exposure.

3.2 Phosphorus Flame Retardants and Plasticizers (PFRs)

Phosphorus flame retardants and plasticizers (PFRs) are mostly applied in polyurethane foam (PUF), thermoplastics, resins, polyvinyl chloride, synthetic rubbers, and textiles [75]. Tris(2-butoxyethyl) phosphate (TBOEP), which is used in waxes, floor polishes, and plasticizers in floor coverings, takes up the highest fraction of PFR concentrations in indoor dust [46]. PFR levels in house dust have been reported in

Table 4 Early-life exposure to phthalates and associations with allergies

Authors (year), country	No. of participants and age	Phthalates in house dust	Phthalates in urine	Results
Bornehag et al. (2004) Sweden	400 (3–8 years)	Dust: DMP, DEP, DiBP, DnBP, BBZP, DEHP, DiNP in children's bedrooms	–	Dust: BBzP was associated with rhinitis and eczema; DEHP was associated with asthma
Kolarik et al. (2008), Bulgaria	102 (2–7 years)	Dust: DMP, DEP, DnBP, BBZP, DEHP, DnOP in children's bedrooms	–	Dust: DEHP was higher in case houses than in control houses. DEHP was associated with wheezing in the 12 months
Beko et al. (2015) Denmark	500 (3–5 years)	Dust: DEP, DiBP, DnBP, BBZP, DEHP, DiNP in children's bedrooms	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP	Dust: DEHP and wheezing, DnBP, BBzP and asthma, rhino-conjunctivitis, atopic dermatitis were associated
			Daily intakes of DEP, DnBP, DiBP, BBzP, DEHP	Urine: MEP and atopic dermatitis were positively associated
Hsu et al. (2012) Taiwan	101 (3–9 years)	DMP, DEP, DBP, BBZP, DEHP, DiNP in children's activity rooms	MMP, MEP, MBP, MBzP, MEHP, MEHHP, MEOHP	Dust: BBzP increased risks of rhinitis and eczema.
				Urine: No association
Ait Bamai et al. (2014) Japan	526 inhabitants of new detached houses	DMP, DEP, DiBP, DnBP, BBZP, DEHP, DiNP in living room	–	Dust: DiBP and DnBP were associated with asthma, DEHP with allergic conjunctivitis, and DnBP, BBzP, and DEHP with atopic dermatitis. Associations were stronger in children than in adults
Ait Bamai et al. (2016) Japan	184 (6–12 years)		Daily intakes of DnBP, DiBP, BBzP, and DEHP	Dust: DEHP was associated with rhino-conjunctivitis
				Urine: No association
Bi et al. (2018) USA	54 children (mean age, 10.3 years) living in low-income homes	Dust: DMP, DEP, DnBP, BBZP, DEHP, DnOP in children's bedrooms	–	Dust: DEHP was associated with childhood asthma severity in summer
Bertelsen et al. (2013) Norway	623 (10 years)	–	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCPP, MCOP, MCNP	Current asthma was associated with the highest quartiles of MCOP and MCNP

Table 5 Early-life exposure to phosphorous flame retardants and associations with allergies

Country	No. of participants and age	PFR	Outcome	Result
Japan, 2009–2010	128 (6–12 years)	TMP, TEP, TPP, TNBP, TCIPP, TCEP, TEHP, TBOEP, TDCIPP, TPHP, TMPP	Asthma, rhino-conjunctivitis, atopic dermatitis	TDCIPP in floor dust and eczema were strongly associated
				TDCIPP in house dust and urinary TDCIPP, TBOEP, and TCIPP metabolites were associated with allergies in children
USA, 2014–2015	54 children (mean age, 10.3 years) living in low-income homes	TNBP, TCIPP, TBOEP, TPHP, TDCIPP	Asthma, asthma symptoms	No association
Sweden	220 (110 children who developed asthma at 4 or at 8 years and 110 matched controls)	TCEP, TCIPP, TDCIPP, TBOEP, TPHP, EHDPHP, mmp-TMPP	Asthma at 4 or 8 years	Levels of TPHP and mmp-TMPP in dust were higher in control samples than in samples collected from homes of asthmatic children

several studies; however, human biomonitoring data is still rather limited. Studies investigating associations between PFRs and allergies are also very limited for both epidemiological and experimental studies (Table 5). Tris(1,3-dichloroisopropyl) phosphate (TDCIPP) found in dust was linked to noticeable rises in ORs of atopic dermatitis/eczema among elementary school children. Furthermore, in the same population, urinary TDCIPP, tris(2-chloroisopropyl) phosphate (TCIPP), and TBOEP metabolites were linked to eczema and/or rhinoconjunctivitis among elementary school children [4]. Metabolites of triphenyl phosphate (TPHP) and 2-ethylhexyl phenyl phosphate (EHPHP) and bis(2-butoxyethyl) phosphate (BBOEP) were linked to increased levels of oxidative stress biomarkers [2]. The allergy-inducing mechanisms of PFRs remain unclear. TBOEP, TCIPP, and TDCIPP cause mild to moderate skin irritation in rabbits [81, 82], while TCIPP and TDCIPP cause skin and eye irritation in rats [75, p. 1213]. A transcriptome study illustrated hepatic pro-inflammatory influence of TBOEP on the immune responses as well as on the lipid and steroid hormone metabolism [52]. Under in vitro conditions, TDCIPP and TPHP were found to be immunocytotoxic and induced oxidative stress [13]. Moreover, TDCIPP had antagonistic effects on androgen receptors, glucocorticoid receptors, and pregnane X receptors (PXRs). TBOEP and TCIPP also exhibited antagonistic activity against PXR [50]. These effects suggest that certain PFRs are likely to be endocrine disruptors. Nevertheless, the mechanisms underlying the immunological effects of PFRs in humans remain unknown. Further experimental and epidemiological researches are urgently required to elucidate these mechanisms.

3.3 Bisphenols (BPs)

Bisphenol A (BPA), a man-made chemical that is widely used for polycarbonate plastics and epoxy resins, can be found in certain food and beverage packaging, dental sealants, and receipts. With rising concerns regarding endocrine-disrupting effects on humans, the use of BPA in products has been phasing down, and other analogues, i.e., bisphenol F (BPF) and bisphenol S (BPS), are being used instead. Due to its widespread use, BPA is detected in more than 90% of human urine samples in Canadians [12], US children [59], and Asian populations (i.e., Chinese, Vietnamese, Malaysians, Indian, Japanese, and Korean people) [87]. Recent reviews have suggested that early-life exposure to BPA is linked to altered neurological developments leading to behavioral problems, low fetal growth, low birth weight, and thyroid dysfunction [9, 10, 66]. In regard to asthma, allergies, and immunological effects on humans, several epidemiological studies have been conducted. In a birth cohort of the Health Outcomes and Measures of the Environment (HOME) study, urine samples were collected from pregnant women twice during pregnancy (at 16 weeks and 26 weeks of gestation), and BPA levels were measured in each sample [69, 70]. Parent-reported child wheeze was assessed every 6 months until they were 5 years-old. Lung function was also assessed when the children were 4 and 5 years old. Maternal mean urinary BPA concentrations were not linked to wheeze under 3 years old; however, they were marginally linked to increased risk of wheezing at 5 years old. Moreover, maternal mean urinary BPA concentrations were linked to decreased lung function at 4 years old, but no relation was found at 5 years old. Urinary BPA concentrations in samples collected at 16 weeks, but not 26 weeks, were linked to increased risk of wheeze. Child urinary BPA concentrations were not linked to lung function or wheeze. Gascon et al. reported that prenatal exposure to BPA was linked to increased risk of wheeze as well as bronchitis under 7 years old [29]. Another birth cohort study in the USA reported that prenatal exposure to BPA was inversely linked to a risk of wheeze among 5-year-old children [26]. In the same study, postnatal exposure to BPA was also investigated. The data show that urinary BPA concentrations in 3-year-old children were linked with wheeze at 5 and 6 years of age. These epidemiological studies investigated both prenatal and postnatal exposure to BPA; however, the findings are inconsistent in each study. This may be due to BPA has a short half-life, resulting in variability in urinary BPA concentrations within and between days [10, 11, 74]. An additional confounding factor is that the timings of urine collections from pregnant women in these studies are different. Spanier et al. and Gascon et al. collected spot urine samples during the first and third trimester of pregnancy, and they used average concentrations of BPA as exposure assessments, while Donohue et al. collected samples during the third trimester.

Several experimental studies haves been suggested some direct mechanistic links between prenatal exposure to BPA and the influence on immune system. For example, pre- and postnatal developmental exposure to 50 μg/kgBW/day enhanced lung inflammation in the mucosal sensitization model [5]. Yang et al. demonstrated

that prenatal exposure to BPA influences asthma risk through upregulation of Th2 pathways and possibly reduces regulatory T-cell counts [85]. Another possible mechanism suggests that BPA may bind to estrogen receptors to disrupt estrogen function and the response of immune cells [3]. However, regarding the other bisphenol analogues (e.g., BPF and BPS), no clear mechanism of action has been defined because of the limited research in this area. Although exposure levels of BPF and BPS are lower than BPA, it has been suggested that BPS and BPF could have equivalent or even greater toxicity than BPA [66]. In addition, the production and usage of BPA are reducing; however, BPF and BPS are increasing. Further epidemiological and experimental studies including other bisphenol analogues are needed to investigate both in detail.

4 Conclusions

In this section, the current epidemiological knowledge regarding the possible influence of environmental chemicals on childhood allergies were summarized. In spite of reported inconsistencies of the immunosuppressive effects of longer carbon-chain PFAS, PFOS, and PFOA, they showed consistent immunosuppressive effects on humans, which decreased risk of allergies and increased the risk of infectious diseases. Prenatal exposure to PCBs/PCDDs/PCDFs may modify the immune responses of children born to exposed mothers. Moreover, these children are at an increased risk of allergy and infection in their childhood and adolescence. Currently, there is insufficient evidence for the long-term effects of PCBs/PCDDs/PCDFs. Some BFRs have been banned due to widespread contaminations and concerns regarding the adverse health effects (e.g., neurodevelopment and reproductive) of BFRs in people. Despite a number of experimental and epidemiological studies, conclusive evidence on immune functions and allergies is very much lacking. Precise exposure assessment of short half-life compounds such as phthalate, PFRs, and bisphenols using human urine samples is difficult which may have led to inconsistent results within each epidemiological study. Nevertheless, even with the limited amount of available data, epidemiological and experimental studies have displayed that PFR exposure from house dust increases the risk of asthma and allergies in childhood. The influence of BPA on the developmental immune system is consistent within experimental studies; however, other bisphenols such as BPF and BPS have not yet been evaluated. Further investigation of the effects of these environmental chemicals, as well as alternative chemicals, on asthma and allergies are essential.

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