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# Emerging contaminants and their impacts on atopic dermatitis: Current mechanisms and future perspectives

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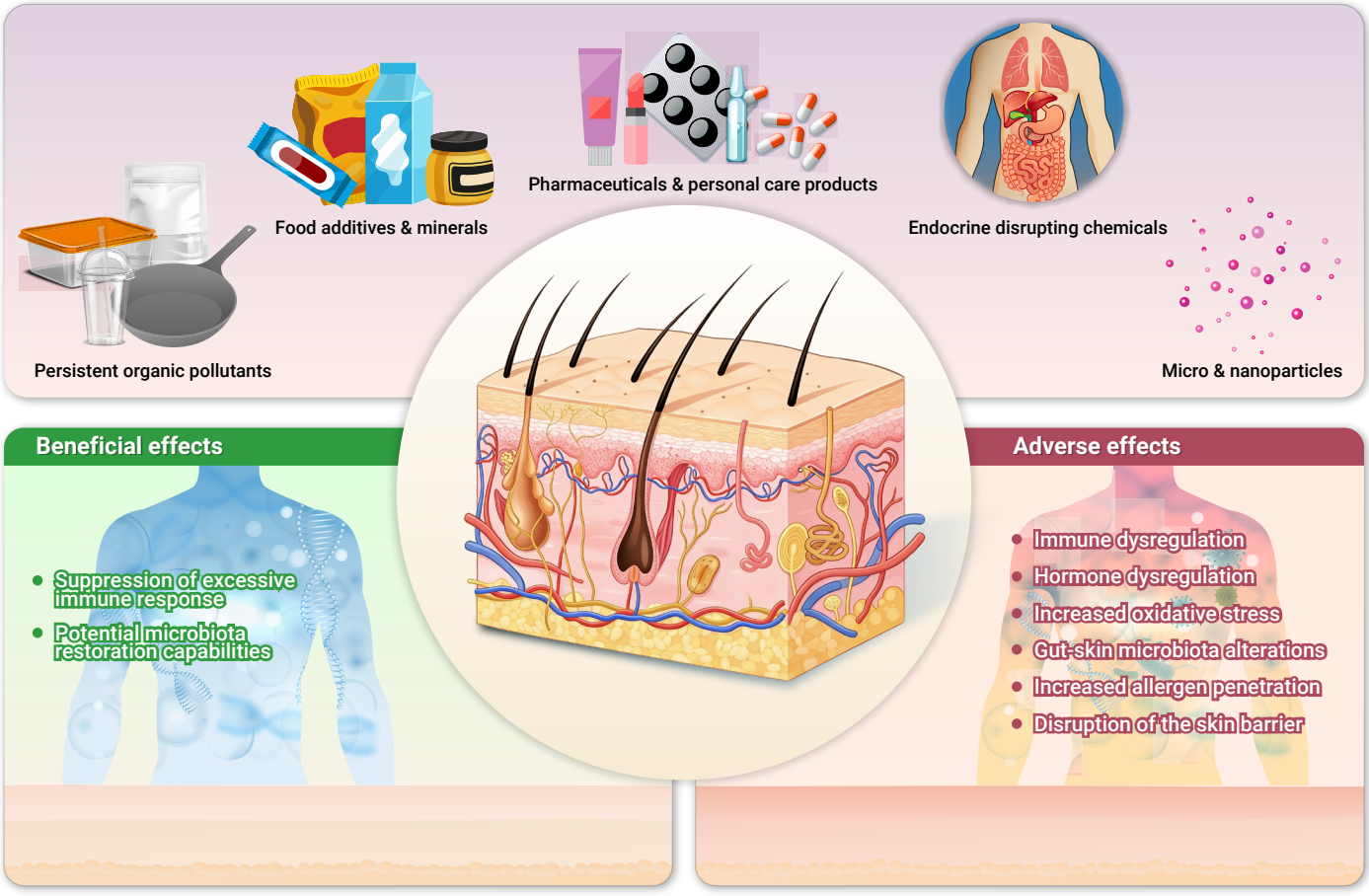
## GRAPHICAL ABSTRACT




## PUBLIC SUMMARY

- Definitions of emerging contaminants (ECs) are changing with the times.
- ECs exhibit varied effects on atopic dermatitis, showing both exacerbating and protective potential.
- Recommendations for the optimization of living environments and lifestyles are presented from the EC perspective.
- Future research should focus on identifying high-priority ECs and their synergistic effects on AD.

REVIEW Evidence-Based Medicine



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With the progression of industrialization and urbanization, the diversity and concentration of emerging contaminants (ECs) in the environment have risen concomitantly. Atopic dermatitis (AD) is a chronic inflammatory skin condition driven by genetic and environmental factors. Research on the interactions between ECs and AD has expanded significantly in recent decades. This review examines the complex interplay between representative environmental ECs and AD, focusing on mechanisms of immune disruption, including Th2 polarization and aryl hydrocarbon receptor (AhR) activation. Drawing on recent evidence, we further identify critical research gaps to guide future investigations into the impacts of ECs on AD, highlight clinical implications and propose potential strategies for exposure reduction and lifestyle adjustments to prevent and manage AD.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease.[1] The overall prevalence of AD is 2-3% and more than 171 million individuals are affected.[2,3] Its pathogenesis is complex, involving both genetic and environmental factors.[4] Alongside the process of industrialization and urbanization, the prevalence of allergic diseases has risen at a pace that genetics alone cannot explain.[5-7] This rise has coincided with increased human exposure to certain emerging contaminants (ECs), which may underlie, at least in part, the marked increase of AD over the past century.[8-11]

Notably, since the 1960s, concentrations of several environmental contaminants have declined, with lead pollution serving as a representative example. The *Lancet* Commission on pollution and health reported that, following the global phase-out of leaded gasoline, blood lead levels in children have decreased markedly worldwide, accompanied by a reduction in the incidence of lead poisoning.[12] Similarly, decreasing trends in air pollutant concentrations have been observed at regional and local scales in Europe.[13] Concentrations of sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), $PM_{10}$, and $PM_{2.5}$ have all declined over the recent decades.[14,15] Such reductions in some environmental contaminants may warrant further investigation.

ECs comprise a diverse group of substances in the environment that pose potential or newly identified hazards to ecosystems and human health. A great number of ECs have been recently identified as harmful due to increasing exposure doses or advances in detection technology. They encompass both natural and synthetic substances that are widely distributed throughout the environment (Figure 1).[16] Common categories include persistent organic pollutants (POPs), endocrine disrupting chemicals (EDCs), food additives and so on (Figure 2). The rapid growth of industrial sectors such as electronics and plastics has led to the use of more than 35,000 chemicals to improve the performance of their products.[17] Some of these chemicals, including plasticizers and microplastics, may have negative impacts on ecosystems and human health.[18,19] In addition, ECs engage in vivo interactions and exert substantial effects on the immune system and allergic reactions, which warrants further attention.

The immune system and inflammatory responses constitute a key mechanistic link between AD and ECs.[20-24] For example, exposure to per- and polyfluoroalkyl substances (PFAS) during infancy and childhood has been shown to be immunosuppressive in humans, leading to an increased incidence of respiratory infections.[25] Alterations in chronic inflammatory status induced by ECs are also commonly observed. Mice exposed to microplastics (MPs) exhibit overproduction of interleukin (IL)-17A via Th17 cells and trigger a downstream inflammatory response.[26] Contaminants such as phthalates may alter intestinal flora and induce intestinal inflammation.[27,28] Specifically, exposure to 0.1 mg/kg dibutyl phthalate increased the relative abundance of *Firmicutes* and *Proteobacteria*, while decreasing that of *Bacteroidetes* and *Verrucomicrobia*, in the gut microbiota, along with elevated levels of inflammatory cytokines such as IL-6 and IL-1β.[28] Moreover, ECs can induce the production of ROS in vivo, which in turn activates molecules such as NF-κB and AP-1, and is associated with inflammation, tumor formation, and other pathological outcomes.[29-31] Certain contaminants, including particulate matter and ozone, have been found to induce ROS, which may activate sensory neurons via redox-sensitive cation channels, thereby triggering dermatitis pathogenesis.[32,33] ECs in food additives, such as glutamates and sulfites, can act as allergens in vivo. They can affect the immune system and food allergies, which are linked to the atopic march.[34]

The potential mechanism between AD and ECs also involves interactions between immune responses and the epithelial barrier. The epithelial barrier is not only a physical defense against environmental factors, but also the site of many immune responses. When the epithelial barrier is compromised, allergens and pathogens can penetrate the skin more easily and trigger type 2 immune responses.[35] Exposure to some ECs that function as allergens increases the level of allergen-specific immunoglobulin E (IgE), promoting the development of AD.[36] Following the onset of immune abnormalities, allergenic stimulation leads to further weakening of the epidermal barrier, which serves as a critical factor in the development of AD, thereby exacerbating immune dysregulation.[37]

Microbiota is also a key mediator across these processes. ECs are associated with microbiome, encompassing both gut and skin microbiota.[38] For gut microbiota, for example, microplastics have been shown to reduce some beneficial taxa, including *Blautia*, in mice.[39] *Blautia* has been reported to suppress the elevation of inflammatory cytokines, including IL-6 and TNF-α, and to reduce excessive oxidative stress.[40] Regarding skin microbiota, Roslund et al. reported that higher soil polycyclic aromatic hydrocarbons levels were associated with *Mycobacterium* on the skin, which may disrupt redox balance and damage the skin barrier.[41] *Mycobacteria* may also promote the differentiation of Th1 cells and regulatory T cells, thereby counteracting the Th2-polarized immune responses that drive AD.[42] Taken together, ECs may alter the composition of both skin and gut microbiota, thereby influencing the gut–skin axis, modulating immune maturation and tolerance, and impairing epidermal barrier integrity.[43]

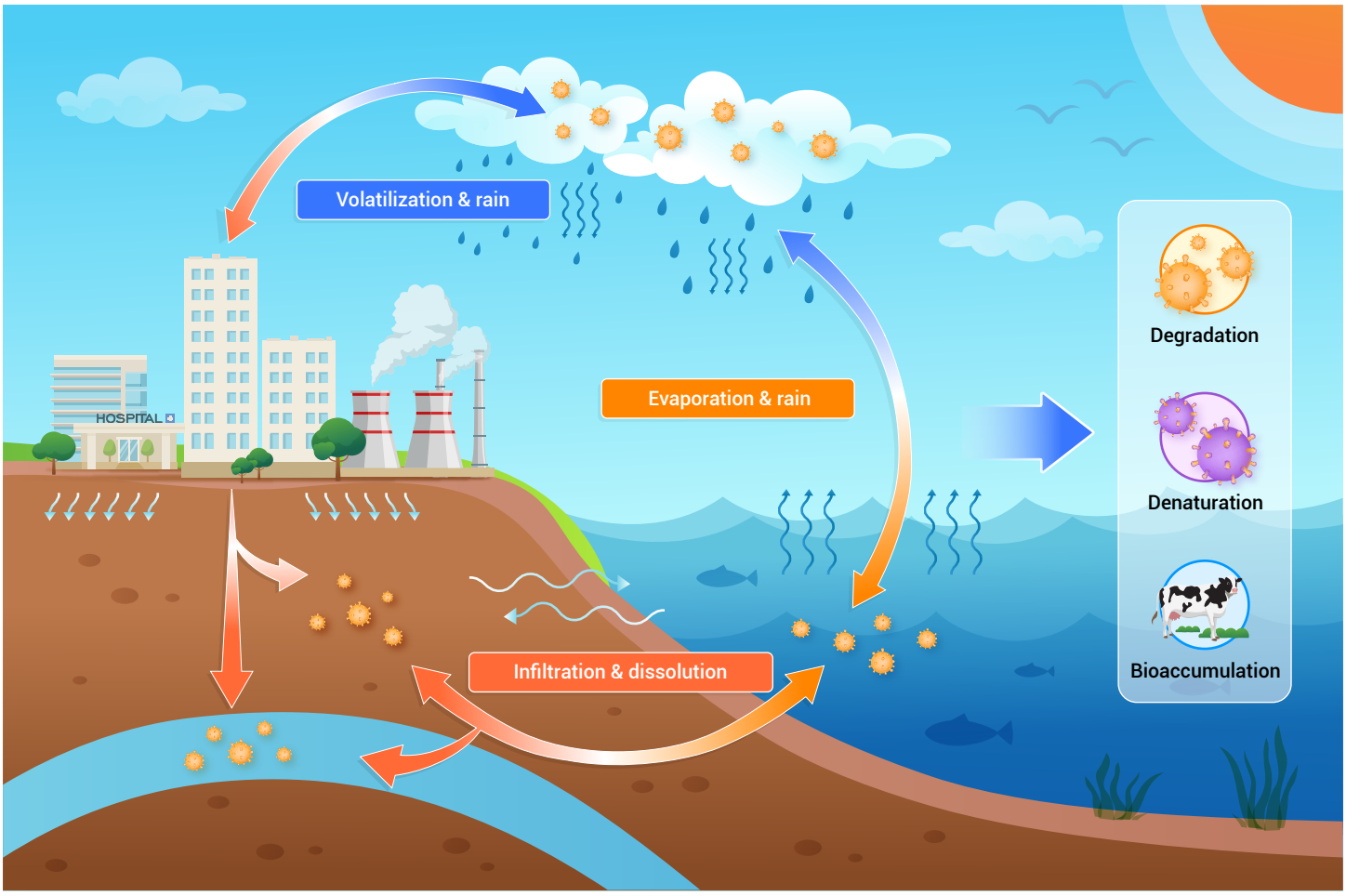


**Figure 1. Pathways through ECs and the environment** The ECs usually come from factories, hospitals, and households. Once released, they transform and accumulate easily in air, soil, and water. Given the difficulty of avoiding or eliminating environmental EC exposure, we recommend reducing the production and emission of ECs at the source.

In this review, we focus on the epidemiological evidence and molecular mechanism studies between AD and ECs. We aimed to provide new insights on clinical management and to offer additional evidence to guide lifestyle adjustments among AD patients.

## PERSISTENT ORGANIC POLLUTANTS (POPs)

### Introduction of POPs

Persistent organic pollutants (POPs) are a class of synthetic chemicals characterized by pronounced environmental and biological persistence. Representative compounds include polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), polychlorinated dioxins and furans (PCDD/Fs), and per- and polyfluoroalkyl substances (PFASs).[44] POPs are ubiquitous across diverse environmental media, and human exposure may occur through multiple pathways. Notably, POPs are bioaccumulative, as they are readily absorbed and accumulated in adipose tissues.[45] Previous studies have found that POPs are associated with a variety of adverse health outcomes, including cancer, allergies, and immune system disorders.[45,46]

### Polychlorinated biphenyls (PCBs)

PCBs are organochlorine compounds extensively used worldwide as plasticizers, flame retardants, and paint additives.[47] PCBs have been inversely correlated with AD in some in vitro studies,[48,49] but some findings have indicated no significant correlation.[50-52] PCBs exposure may alter immune homeostasis, enhancing Th1 immune responses while suppressing Th2 immune responses.[49] PCBs have also been shown to increase IL-6 and IL-8, thereby activating the aryl hydrocarbon receptor (AhR) (Figure 3). AhR is highly expressed in the acutely diseased skin lesions of patients with AD and psoriasis, and its activation may be associated with an elevated risk of AD.[53] In conclusion, the relationship between PCBs and AD warrants larger-scale studies. However, the imbalance between Th1 and Th2 immunity and AhR pathway activation are considered key potential mechanisms underlying the effect of PCBs on AD.

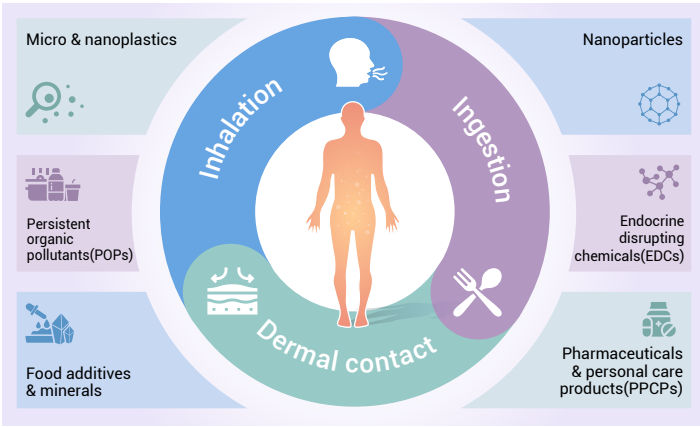


**Figure 2. The common ECs and exposure ways** There are three primary routes of human exposure to environmental pollutants: inhalation, ingestion, and dermal contact. And the most common ECs include persistent organic pollutants (POPs), endocrine-1disrupting chemicals (EDCs), food additives and minerals, nanoparticles, micro- and nanoplastics, and pharmaceuticals and personal care products (PPCPs). Each of these exposure routes is associated with all categories of ECs.

### Per- and polyfluoroalkyl substances (PFASs)

PFASs are chemicals commonly used in products such as non-stick cookware, waterproof clothing, food packaging, and firefighting foams, owing to

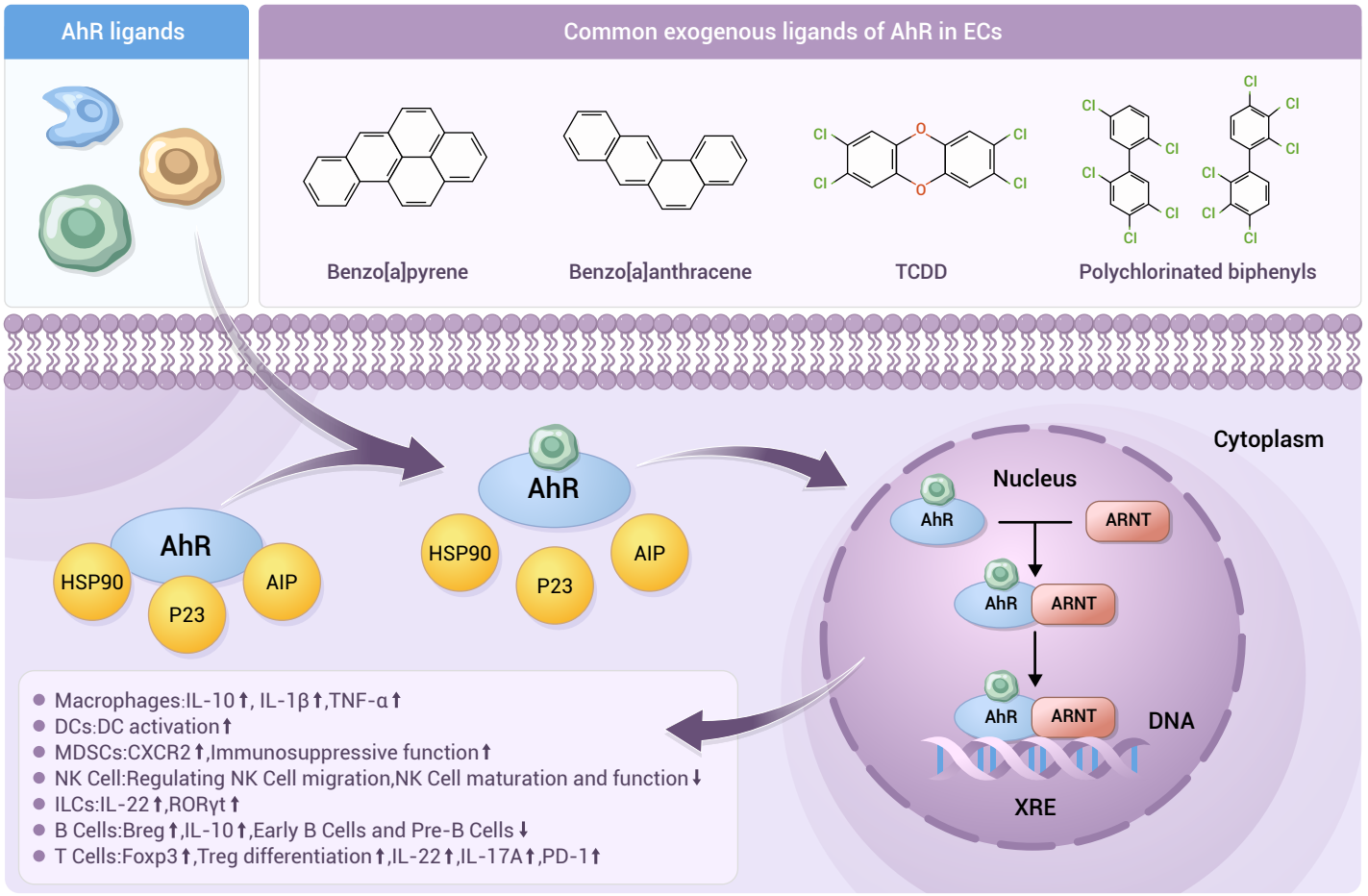


**Figure 3. Aryl Hydrocarbon Receptor (AhR) activation by ECs** This schematic illustrates the cellular mechanism underlying AhR activation by common ECs. Upon ligand binding, AhR translocates into the nucleus, where it forms a complex with ARNT.[203] This complex then binds to xenobiotic response elements (XRE) in DNA, regulating transcription of immune-related genes.[204,205] This pathway modulates immune cell functions by influencing cytokine secretion (e.g., IL-10, IL-1β, IL-17, IL-22).[206,207] It also alters dendritic cell activity and MDSC-mediated immunosuppression.[207,208] AhR, aryl hydrocarbon receptor; HSP90, heat shock protein 90; P23, protein 23; AIP, aryl hydrocarbon receptor interacting protein; ARNT, AHR nuclear translocator; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; DNA, deoxyribonucleic acid; XRE, xenobiotic response element; ECs, endothelial cells; DCs, dendritic cells; MDSCs, myeloid-derived suppressor cells; CXCR2, C-X-C motif chemokine receptor 2; NK cells, natural killer cells; ILCs, innate lymphoid cells; RORγt, RAR-related orphan receptor gamma t; Breg, regulatory B cells; T cells, T lymphocytes; Foxp3, forkhead box P3; IL-10, interleukin-10; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-22, interleukin-22; IL-17A, interleukin-17A; PD-1, programmed cell death protein 1.

their water- and oil-repellent properties.[54] PFASs encompass a structurally diverse group of compounds, exhibiting considerable variation in chemical structures and properties.[55] Most PFAS members are resistant to degradation, bioaccumulative, and are ubiquitous in air, water, and biota.[56] A number of cohort-based studies have been conducted in humans. Perfluorooctanoic acid (PFOA) has been positively correlated with serum IgE levels and shown to increase the risk of AD in childhood.[56-58] And this effect was more pronounced in children carrying *GSTT1*-deficient or *GSTM1*-deficient genotypes,[57] suggesting gene–environment interactions. Perfluorooctane sulfonate (PFOS) is also positively associated with AD.[59] In addition, Rudzanova et al. found a sex-specific association between PFOS and atopic eczema, with negative effects on women and positive effects on men.[20] This may be attributable to the potential endocrine-regulating function of PFASs.[60,61] By contrast, Kvalem et al. reported that perfluorononate (PFNA), perfluorodecanoate (PFDA), and perfluoroundecanoate (PFUnDA) were negatively correlated with AD in girls, indicating that different types of PFASs involve different mechanisms and effects.[62,63]

The effects of PFAS on the immune system have been linked to various cytokines and signaling pathways. In vitro evaluation and in mice, PFOS may increase the secretion of Th2 cytokines (IL-4 and IL-10) and decrease that of Th1 cytokines (IL-2 and IFN-γ), shifting the immune response to the Th2 phenotype and thereby raising the risk of allergic diseases.[64,65] Zhao et al. found through transcriptomics that PFOS can partially interfere with the expression of cytoskeleton-related genes to inhibit cellular ciliogenesis and impede the transduction of pathways such as transforming growth factor β (TGF-β) and NOTCH, which can lead to dermatological diseases.[66] In human cells, PFASs may also affect the peroxisome function and exacerbate DNA damage via increased ROS.[67,68] These effects are much more severe in fetuses and children, underscoring the potential value of minimizing early PFAS exposure in preventing the development of AD in children.

### Phosphorus flame retardants (PFRs)

Phosphorus flame retardants (PFRs) and brominated flame retardants (BFRs) are predominantly used in indoor environments as additives in flame retardants and plasticizers.[69,70] Tris(2-chloro-diso-propyl) phosphate (TCIPP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), DE71 and DE79 (two types of BFRs) have been shown to cause or exacerbate AD.[69,71] A study conducted in children showed flame retardants exert their effects primarily through elevated IgE levels and oxidative stress.[72]

### Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are generated primarily during the incomplete combustion of coal, oil, and gas. They constitute a group of hydrocarbons characterized by multiple benzene rings and are ubiquitous throughout the natural environment, including atmospheric particulate matter, cigarette smoke, barbecue smoke, etc. Due to their lipophilic nature, PAHs tend to accumulate in adipocytes, with older and overweight individuals at correspondingly higher risk.[73] Tang et al. reported elevated urinary concentrations of 9-hydroxyfluorene and 2-hydroxyphenanthrene in patients with AD.[70] Kim et al. investigated the association between urinary PAHs and

Table 1. A summary of different classes of POPs and their main effects on AD.

| POPs | Representative Substances | Main Effects |
|---|---|---|
| Polychlorinated Biphenyls (PCBs) | LC-PCB; PCB-28 | Evidence regarding the impact of PCBs on AD is inconsistent, showing aggravating, protective, or no effects, and further research is needed to clarify this relationship. |
| Per- and polyfluoroalkyl substances (PFAS) | PFOA; PFOS | A positive association between PFAS exposure and AD has been reported, with potential modulation by sex. |
| Flame Retardants (FRs) | PFRs; BFRs | FRs may induce or exacerbate AD by increasing oxidative stress and IgE levels. |
| Polycyclic aromatic hydrocarbons (PAHs) | Hydroxyfluorenes; Hydroxynaphthalene | PAHs have been shown to exacerbate allergic responses, with a potential positive association with AD. |
| DDT and DDE | – | No direct evidence currently links DDT or DDE to atopic dermatitis. |
| Chlorinated paraffins (CPs) | SCCPs | CPs are found to be significantly associated with AD. |

allergic triad symptoms (chronic itching, sneezing, and wheezing) and found that 3-hydroxyphenanthrene (3-PHE) and 1-hydroxypyrene were positively correlated with chronic itching in elderly people.[73] These studies suggest that PAHs may be associated with AD symptoms. The potential mechanisms include chronic AhR activation, impaired regulatory T (Treg) cell function and the increased expression of Th2-related markers, such as IL-4 and IL-13.[74,75] Notably, PAHs are also components of coal tar, which have anti-inflammatory and antibacterial properties when applied topically and has been used in the topical treatment of a variety of dermatological conditions.[76-78] This finding underscores the importance of exposure route in determining the effect of PAHs on skin health.

### Organochlorine pesticides

Regarded as a type of ECs due to their increasing levels, dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) are widely distributed across the globe.[79] Karmaus et al. demonstrated that DDE may attenuate the protective effect of breastfeeding against allergic symptoms in infants.[80] Nonetheless, direct evidence linking DDT and DDE to AD remains currently lacking.

### Chlorinated paraffins (CPs)

Chlorinated paraffins (CPs) represent an emerging class of POPs,[81] and short-chain CPs (SCCPs) are the most toxic subgroup. Huang et al. conducted a cross-sectional study and reported that CPs in ambient PM2.5 were significantly associated with AD and allergic rhinitis.[22] The mechanism may involve CP-induced increases in blood immune cells, which enhance allergic responses.[22] Moreover, the toxicity of CPs may increase when they coexist with other pollutants. The interactions and synergistic effects of multiple contaminants warrant further investigation.[82,83]

In summary, we found that PFASs, PCBs and PAHs have been the focus of research in recent years, with the main conclusions summarized in Table 1. Dysregulation of Th1/Th2 immunity, a rise in oxidative stress, and AhR pathway activation represent three of the most promising avenues for investigating POPs and AD. Sex and body fat percentage also influence the relationship between POPs and AD, which means more detailed research is needed. Overall, reducing exposure to and uptake of POPs is likely to confer health benefits.

## FOOD ADDITIVES AND MINERALS

### Definition of food additives

As defined by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), a food additive is "a substance added to food to maintain or improve its safety, freshness, taste, texture, or appearance". The U.S. Food and Drug Administration (FDA) has approved more than 3,000 food additives. Common food additives include food dyes and spices, preservatives, among others.[84]

### Common food additives with AD

Food dyes have been implicated as potential contributors to the pathogenesis of AD and allergic disease. Specifically, carmine and tartrazine have been associated with allergic reactions,[85,86] resulting in intermittent episodes of atopic eczema in children.[87] Patients with AD have been reported to exhibit a statistically significant increase in positive allergic reactions to food additives.[88] Notably, a high prevalence of positive atopy patch test (APT) reactions to azorubine has been observed, alongside significantly higher consumption of fruit yogurts, ice cream, jams, and cakes among AD patients, suggesting that azorubine may contribute to AD pathogenesis.[89]

A diverse range of preservatives is used in food.[90] Sulfite agents and parabens are commonly used as preservatives across the food and pharmaceutical industries. With regard to studies in humans, Worm et al. extracted peripheral blood leukocytes from AD patients presenting with food intolerance. After stimulating the cells with different food additives, they observed thioleukotriene generation, revealing that lemon yellow, benzoates and nitrites alone increased sulfidoleukotriene (sLT) production in peripheral leukocytes. The authors hypothesized that increased sLT may serve as one of the mechanisms of AD exacerbation.[91]

Food contaminants comprise substances capable of contaminating food during production and processing, such as pesticide residues. Pesticides and herbicides have been shown to be associated with atopic diseases.[92] Rodrigues et al. reported that exposure to pesticides increased the risk of asthma onset or exacerbation in children and adolescents, but there was no evidence of an association between exposure to pesticides and atopic dermatitis in children and adolescents.[93] By contrast, Neonicotinoids (NN) target nicotinic acetylcholine receptors (nAChRs) expressed on immune cells, and nAChRs have anti-inflammatory effects.[94] Ishida et al. administered clothianidin (CLO) to male NC/Nga mice with induced AD and found that CLO increased total plasma IgE levels but decreased epidermal thickening, mast cell counts, and plasma histamine levels during the early stages of AD. These findings suggest that CLO may suppress the early symptoms of AD.[95] Given that pesticide and herbicide residues in food are subject to strict regulatory control, low-level but long-term exposure may warrant greater attention.[96]

### Minerals

Minerals are natural constituents of the Earth's crust, yet their accumulation at excessive concentrations may pose substantial ecological risks. With the progress of urbanization and industrialization, the environmental pollution attributable to toxic minerals has become increasingly severe.[97] For instance, urbanization requires people to extract more arsenic-rich geological material for use as fill material in the construction of residential and industrial facilities, thereby increasing human exposure risk to arsenic.[98] Rehman et al. examined urban particulate matter (PM) armored with potentially toxic metals and found industrial areas had high levels of cadmium (Cd) and chromium (Cr).[99] Therefore, many minerals are also regarded as constituents of the broader category of ECs. A summary of the mineral-related findings is presented in Table 2.

Heavy metals, to some extent, may also serve as inspirations for, and key components of, novel therapeutics. Hollow manganese dioxide nanoparticles (H-MnO 2 NPs), an inorganic nanoparticle, can efficiently scavenge ROS.[100] In animal models, H-MnO 2 -Gel reduced skin thickness, mast cell counts, IgE antibody levels and inflammatory Th2 cytokines, while promoting the regeneration of inflamed tissues and enhanced the recovery of AD-affected skin. These findings suggest that H-MnO 2 gel can improve AD symptoms.[101] In addition, studies have shown that topical strontium salts are effective in reducing histamine-induced and IgE-mediated itch in humans. Papoiu et al.

Table 2. Health effect of Minerals in AD.

| Contaminant | Experiment Model/ Human Group | Route of Exposure | Exposure time/dose | Impact on AD | References |
|---|---|---|---|---|---|
| Manganese dioxide | The mouse fibroblast cell line (L929); Female 6-week-old BALB/c mice | Skin exposure | H-MnO2-Gel (approximately 5 mm in diameter and 1 mm in thickness) | Clears ROS and regulates the inflammatory microenvironment, providing a promising approach for the treatment of AD. | 101 |
| Manganese | Children from the EDEN birth-cohort | / | / | Associated with greater risk of eczema | 103 |
| Methylmercury | Families in NICE study | / | / | Increase the risk of AD | 104 |
| Methylmercury | A birth cohort in the Faroe Islands | / | / | Positively associated with grass-specific IgE concentration | 48 |
| Mercury | 1,751 pregnant women from Mothers and Children's Environmental Health cohort study | / | / | Increase the risk of AD | 109 |
| Mercury | 94,794 mother-infant pairs in the Japan Environment and Children's study | / | / | Not associated with the risks of any allergic disease | 112 |
| Mercury | Adult population of the Republic of Korea | / | / | Positively associated with lifetime prevalence of AD | 111 |
| Mercury | Children from the Korean National Environmental Health Survey (KoNEHS) | / | / | Exacerbate symptoms of AD | 209 |
| Mercury | All school beginners in Augsburg, Bavaria, in 1996 | / | / | Increase the risk of AD | 210 |
| Cadmium | Children from the EDEN birth-cohort | / | / | Associated with greater risk of asthma, eczema and food allergy | 103 |
| Cadmium | Mother and children from the Mothers' and Children's Environmental Health (MOCEH) study | / | / | Significantly associated with the presence of AD in 6-month-old infants | 211 |
| Cadmium and Arsenic | 370 mother and child pairs from the original Taiwan Maternal and Infant Cohort Study | / | / | Coexposure to inorganic arsenic and cadmium increase the risk of AD. | 212 |
| Lead | 738 mother-child pairs from the MOCEH study | / | / | Increases risk of AD in 6-month-old boys | 213 |
| Lead | 22 houses in Jeju island, South Korea | / | / | Associated with atopic dermatitis symptoms | 214 |
| Lead | Women and children from COCOA study | / | / | Associated with the duration and severity of AD | 107 |
| Lead | 110 patients with eczema and 41 patients with miscellaneous skin conditions | / | / | Have significant correlations with disease severity, quality of life and atopy | 105 |
| Lead | Adults from Korea Center for Disease Control and Prevention | / | / | Associated with asthma, atopic dermatitis, and allergic multi-morbidit | 215 |
| Chromium | Women and children from COCOA study | / | / | Associated with the duration and severity of AD | 107 |
| Hexavalent chromium [Cr(VI)] | Dermatitis patients in southern Sweden | / | / | Increase the risk of AD | 216 |
| Arsenic | 300 healthy mother–child pairs from the POSGRAD clinical trial study | / | / | Marginally significant associated with AD | 114 |
| Arsenic | A Taiwanese birth cohort | / | / | Increase the risk of a CB-tIgE level higher than 1 IU/mL | 113 |
| Arsenic trioxide | HaCaT keratinocytes | / | A very low-dose 0.5 ppm | Aids cell growth but disrupts the DNA transcription process | 217 |

found that a 4% topical strontium hydrogel formulation (TriCalm®) exhibited significant antipruritic activity against both histamine-mediated pruritus, and non-histaminergic itch mediated by the PAR2 pathway.[102]

Manganese (Mn), lead (Pb), Cr, and Cd are all common heavy metal contaminants. Numerous epidemiological studies have examined their associations with AD. Elevated Cd levels in pregnant women are associated with an increased risk of eczema and food allergies.[103,104] Pb levels have been shown to be significantly correlated with AD severity, quality of life, and allergic symptoms.[105] Nickel, chromium salts, and Mn salts are common causes of allergic labyrinthitis,[106] supporting their potential to induce allergic reactions. AD severity has also been shown to be positively correlated with the chromium concentration in human cord blood.[107] IL-13 in cord blood mononuclear cells (CBMC) was positively correlated with lead and chromium levels in cord blood. The mechanism may be an immune response affecting

Th2 polarization.[107] In addition, manganese ions have a bactericidal effect, too. Manganese and iodide ions under acidic conditions (pH 2.0-3.0) act synergistically against *staphylococci*. Accordingly, acidic solutions containing manganese and iodide ions may hold clinical utility in the treatment of skin diseases caused by *Staphylococcus aureus*.[108]

Mercury and arsenic are toxic minerals. Mercury exposure increases the risk of AD in both adults and children.[109-111] Mercury also interacts with other elements in the human body. Maternal blood mercury concentrations modify the relationship between prenatal selenium exposure and atopic dermatitis in early childhood. The inverse association between selenium and AD was more pronounced at lower levels of mercury exposure. A potential biological mechanism underlying the interaction between mercury and selenium exposure involves the formation of Hg-Se complexes, which inhibit the activity of selenium-containing proteins (e.g., glutathione peroxidase), thereby increasing oxidative stress and inflammation.[112]

Arsenic exposure during pregnancy has been shown to increase the risk of elevated cord blood total immunoglobulin E (CB-tIgE) levels, thereby raising the risk of atopic dermatitis in children.[113] Omega-3 fatty acid supplementation during pregnancy may alter this association.[114]

In summary, one of the primary mechanisms underlying the effects of minerals on AD is their action as sensitizers. Therefore, minimizing exposure to harmful minerals is advisable. Although minerals have many important effects on AD, Hon et al. found that serum heavy metal levels in patients with eczema usually do not exceed the local toxicity reference range.[105] This finding suggests that stricter dosage standards for certain minerals may warrant consideration in pregnant women and children.

## PHARMACEUTICALS AND PERSONAL CARE PRODUCTS (PPCPs)

### Introduction of PPCPs

Pharmaceuticals and personal care products (PPCPs) are a large group of ECs that cover a wide range of chemicals found in drugs, antiseptics, care solutions, and cosmetics. In this part, we focus on preservatives and antibiotics. More than 6 million PPCPs are currently available on the market and have been detected in water, soil and air.[115] Documented adverse effects include damage to DNA structure,[116] carcinogenicity,[117,118] allergy reaction,[119,120] and other toxicological endpoints.

### Preservatives

Since emollients and moisturizers are frequently used by AD patients, preservatives in skin care products for AD deserve to be scrutinized. Methylchloroisothiazolinone (MCI), methylisothiazolinone (MI), benzophenone, avobenzone, and butylated hydroxytoluene are common preservatives found in lotions and cosmetics.[121] MCI and MI in lotions upregulate IL-4 and IL-13 expression and activate M2 macrophages, thereby exacerbating AD.[122] Benzophenone and avobenzone in sunscreens are also recognized as common allergens, inducing contact dermatitis in humans.[123] Regulatory differences, such as stricter EU limits on MCI/MI compared to the US, influence exposure levels.[124]

### Antibiotics

Antibiotics are a group of PPCPs and have also been classified as a category of ECs.[125] Exploring how antibiotics influence the development of AD not only enhances treatment efficacy but also facilitates efforts to address the pollution arising from antibiotic overuse. Given the abundance of relevant research, antibiotics have already been the subject of dedicated reviews.[126-128]

Antibiotics may assist in the treatment of AD through the reduction of bacterial colonization.[129] However, cohort studies have demonstrated a link between antibiotic exposure and allergic diseases. Children exposed to antibiotics exhibited a 38% higher likelihood of developing food allergies and AD, with their risk of asthma nearly doubling. However, these associations may vary depending on the timing of exposure relative to the onset of AD.[130] Intrauterine exposure to antibiotics is associated with an increased risk of AD in childhood.[131-135] By contrast, exposure to antibiotics for less than 24 hours during vaginal delivery does not appear to increase the risk of AD.[136] Similarly, systemic antibiotic therapy in the first year of life was associated with a higher AD risk relative to later exposure. Penicillin, in particular, is most strongly associated with AD.[131] The underlying mechanism may involve the skin and gut microbiome.[137] The enrofloxacin use during pregnancy in adult mice decreased the relative abundance of *Clostridium cluster IV*, which can increase intestinal TGF-β levels and promote the development of inducible IL-10-producing Treg cells.[138]

In conclusion, early antibiotic exposure appears to increase the risk of AD overall. Physicians should be more cautious when using antibiotics in patients with AD because bacterial resistance occurs frequently and with more severe consequences in this population.

## ENDOCRINE DISRUPTING CHEMICALS (EDCs)

### Introduction of EDCs

Endocrine disrupting chemicals (EDCs) are a diverse group of substances that bind to hormone receptors or interfere with hormone metabolism.[139] The most extensively studied EDCs include bisphenols (BPs), phthalate acid esters and so on.[140] Human exposure to these compounds is largely unavoidable in daily life. EDCs can interfere with or mimic hormones, activating various signaling pathways. The health risks of exposure to EDCs are closely linked to specific life stages.[141] During pregnancy, estrogen and progesterone play important roles in endocrine regulation. Given the mechanism of action of EDCs, embryonic development and early life stages undoubtedly represent a critical window of exposure to these compounds in humans. Exposure of fetuses and young children to EDCs via maternal blood and/or milk may lead to persistent reprogramming of physiological processes.[142] Relevant findings on EDCs are summarized in Table 3.

### Bisphenols (BPs)

BPs are able to cross the placental barrier and induce epigenetic changes in the fetus. Common types of BPs include BPA, BPF and so on. Kim et al. identified a range of hypomethylated genes in the bisphenol-exposed group compared to the control group, including *IL4*, *JAK1*, and *IL13RA1*.[143] These genes belong to the PI3K-AKT and JAK-STAT signaling pathways, which regulate the proliferation, survival, and differentiation of keratinocytes via JAK1 phosphorylation.[144] In addition, these genes and pathways are involved in the production and regulation of Th2 cytokines, and bisphenol exposure may exacerbate the symptoms of AD by decreasing methylation and increasing expression of these genes in humans.[143] A prospective cohort study conducted by Li et al. further found that pregnancy exposure to BPA was independently associated with an increased risk of eczema in infants.[145] A similar association was also observed with asthma and allergic rhinitis in children,[146] suggesting that bisphenols may exacerbate allergic diseases.

Conversely, Tajiki-Nishino et al. conducted in vivo experiments using a mouse model of allergic inflammation induced by the Th2-type hemiantigen toluene-2,4-diisocyanate (TDI). Mice were orally administered BPA at 48, 24, and 4 hours prior to TDI stimulation. In this dermatitis model, high doses of BPA significantly reduced the ear swelling response. This suggests that for allergic symptoms, the effects of oral and dermal exposure to BPA may be different.[147]

### Phthalate acid esters

Phthalate acid esters, another class of EDC, are commonly used as plasticizers and are among the most prevalent indoor pollutants.[148] PVC flooring, packaged foods, and pets may all contribute to elevated urinary concentrations of phthalate metabolites, and Di(2-ethylhexyl) phthalate (DEHP) has been identified as a dog allergen.[148-150] Callesen et al. collected urine samples from 440 children aged 3-5 years and found a weak positive correlation between urinary MEP (a simple monoester of phthalates) and AD.[148] The metabolite of monobenzyl phthalate (MBzP) has also been positively associated with an increased risk of developing eczema in early childhood.[151,152] Researchers measured MBzP in late-pregnancy urine samples from 407 women residing in New York City and reported that an increased quartile range of the log concentration of MBzP was positively associated with early-onset eczema.

Furthermore, phthalates may also influence allergic responses more broadly. Alterations in blood levels of Th1 and Th2 cells in children have been associated with exposure to phthalates during pregnancy,[153] and a plausible underlying mechanism involves the negative correlation between benzylbutyl phthalate (BBzP) and thymic stromal lymphopoietin (TSLP) methylation

Table 3. Health effect of EDCs in AD.

| Contaminant | Experiment Model/ Human Group | Route of Exposure | Impact on AD | References |
|---|---|---|---|---|
| Estrogen | Female C57BL/6J mice | Slow-release | Suppresses both acute and chronic itch. | 218 |
| Progesterone and estradiol and free estradiol | Serum from the Finnish Maternity Cohort (FMC) serum bank | / | No association was found between maternal sex hormone and AD | 219 |
| Bisphenol | Pregnant women from the GREEN cohort | / | Hypomethylate the JAK-STAT and PI3K-AKT signaling pathways and have a negative impact on AD through epigenetic mechanisms. | 143 |
| Bisphenol | Children in the 3rd Korean National Environmental Health Survey | / | Positively correlated with AD | 220 |
| Bisphenol | 18 boys with AD (age 3-7 years) in a day care center in Seoul | / | Associated with aggravation of AD symptoms | 156 |
| Bisphenol | BALB/cAnN and C57BL/6J mice | Oral administration | Directly exacerbates allergic airway inflammation but not allergic dermatitis | 147 |
| Phthalate metabolites | Children in the 3rd Korean National Environmental Health Survey | / | Positively correlated with AD | 220 |
| Phthalate metabolites | 18 boys with AD (age 3-7 years) in a day care center in Seoul | / | Associated with aggravation of AD symptoms | 156 |
| Phthalate metabolites | 106 AD children and 347 controls from CEAS cohort | / | Increase the risk of AD | 221 |
| Phthalate metabolites | Children from the Danish Indoor Environment and Children's Health study | / | Have a weak positive association with AD | 148 |
| Phthalate metabolites | 448 school children | / | Significantly associated with skin barrier dysfunction but not with atopic sensitization | 222 |
| Phthalate metabolites | 156 detached dwellings and their 516 inhabitants | / | Associated with the prevalence of AD in children | 223 |
| Phthalate metabolites | A large group of 3-5 year old children | / | Have a stronger effect on sensitization in children with allergic disease | 224 |
| Phthalate metabolites | Mothers and children from the Polish Mother and Child Cohort | / | Increased the risk of food allergy in children | 225 |
| Phthalate metabolites | Children from the Korean National Environmental Health Survey (KoNEHS) | / | Increase the occurrence of allergic symptoms in children | 226 |
| Mono-2-ethyl-5-hydroxyhexyl phthalate | 413 mother-child pairs in the MOCEH study | / | Positively associated with AD | 227 |
| Mono-2-ethyl-5-oxohexyl phthalate | 145 mother-child pairs from the prospective Polish Mother and Child Cohort Study | / | Decrease the risk of AD | 228 |
| Mono-2-ethyl-5-hydroxyhexyl phthalate | 145 mother-child pairs from the prospective Polish Mother and Child Cohort Study | / | Increase the risk of AD | 228 |
| Dibutyl phthalate (DBP) | Male Balb/c mice | Skin exposure | Endow an atopic predisposition | 229 |
| Di-(2-ethylhexyl) phthalate (DEHP) and diisononyl phthalate (DINP) | NC/Nga mice | Oral administration | Increase the allergic response in animal AD models | 230 |
| Di(2 - ethylhexyl) phthalate | Children from kindergartens and daycare centres in Seoul, Korea | / | Exposure level and the age of the subjects can cause different effects. | 231 |
| Di-(2-ethylhexyl) phthalate (DEHP) and diisononyl phthalate (DINP) | Male C3H/HeJ Jcl mice | Intratracheal injection | Modulate neuroimmune biomarkers in the hypothalami of allergic mice | 232 |

levels.[154] TSLP is an IL-7-like cytokine that enhances Th2 cell polarization signaling and provides a microenvironment that triggers dendritic cell-mediated Th2 inflammatory responses, thus inducing naive T cells to differentiate into Th2 cells.[155] The association between urinary phthalate and BPA concentrations and AD symptoms in children was found to be time-dependent, with levels of most phthalate metabolites higher in the morning than in the afternoon, while AD severity was higher in summer than in spring.[156]

To date, research on EDCs has predominantly focused on pregnant women and children, which may be related to hormonal factors in AD. Due to the stimulation of Th2 immune responses by estrogen and progesterone, AD has become the most common dermatosis during pregnancy, accounting for approximately 50% of all pregnancy dermatoses.[157] Therefore, greater caution may be warranted in managing EDC exposure among pregnant women and children. Both BPA and phthalate acid esters can affect gut microbes. Based on this, oral probiotics are worth trying.[158] Moreover, several kinds of EDCs may have joint association in vivo. We should conduct further research to explore it rather than simply summing their individual effects.

## GENERAL ENVIRONMENT

### Introduction of general environment

ECs frequently coexist in the environment, giving rise to synergistic effects that amplify AD risk. For example, CPs combined with PAHs increase toxicity via enhanced AhR activation.[82] These interactions underscore the need for future studies to investigate EC mixtures using advanced exposure assess-

Table 4. Sex-specific effects of ECs on AD.

| EC Category | Main Sex-Specific Effects | Mechanism | References |
|---|---|---|---|
| PFAS | Negative effect on women, positive on men for PFOS. | Differences in PFAS blood concentrations; Interplay between PFAS and sex hormones; Th2 polarization. | 20,56,57 |
| Bisphenols | Increasing the risk of AD. | Mimicking estrogens; Regulating Th2 cytokines. | 143,233 |
| Phthalate acid esters | Positively associated with AD. | Enhancing Th2 inflammatory responses. | 154,155 |

ment techniques, such as metabolomics. Given the frequent interactions among ECs, researchers should consider examining air, water, and consumer products as sources of cumulative exposure. Common examples are occupational environments and residential environments. The advantage of this type of study is that it can synthesize the combined effects of multiple factors, while the disadvantage is that it can only be used with certain groups of people and the specific effects of various substances cannot be determined.

### Occupational environment

Occupational environmental exposures have been strongly associated with AD. However, occupational environments as a whole have been less well studied than individual substances. Exposures in paper mills and animal laboratory settings have both been reported to increase the risk of AD.[159,160] The dental workplace for dentists, technicians and medical students influences allergic disease by causing work-related respiratory symptoms, and both allergic rhinoconjunctivitis and AD are associated with it.[161,162] Some special work environments, such as factories and hospitals, exhibit elevated concentrations of certain chemicals or biological agents that may act as allergens. Possible interactions between ECs in the occupational environment require further study in the future.

### Residential environment

Residents residing near industrial areas have been reported to exhibit more symptoms of AD than control populations.[163] Residential greenery reduces the risk of eczema in young children, with pregnancy appearing to represent the key exposure window.[164] Living next to larger highways also increases AD risk.[165-167]

The residential environment encompasses a range of factors, including indoor air, house dust, and water sources, within which ECs collectively influence AD.[168,169] Childhood eczema was significantly associated with laminate wood flooring use, residence in a villa/townhouse, the presence of mold or damp stains in children's rooms, and infrequent cleaning of children's rooms.[170] Although numerous studies have examined specific ECs within the home environment, more studies are required to be conducted as a whole.[171]

## OTHER ECs THAT ARE DIFFICULT TO CLASSIFY

### Antibiotic resistance genes

Antibiotic resistance genes (ARGs) are widely distributed across various environments, such as surface water, wastewater, and sediment, thereby causing microbial dysbiosis.[172,173] Researchers have identified a series of ARGs that confer resistance to antibiotics in bacteria. These genes can be horizontally transferred among bacteria, complicating clinical treatment, and are increasingly recognized as a distinct category of ECs.

Patients with AD often develop recurrent skin infections caused by *S. aureus*.[174] Strains of *S. aureus* associated with AD often carry multiple ARGs. Kashaf et al. identified the *murQ* locus as being associated with *S. aureus* peptidoglycan metabolism, as well as with the regulation of drug resistance mechanisms.[175]

*NorA* and *qacA* mediate resistance to fluoroquinolones (e.g. ciprofloxacin).[176] In mice, *MgrA* regulates the expression of the *tet38* gene, the overexpression of which confers resistance to tetracycline.[177] *lmrS* multidrug efflux pump and *aac (6')-Ie -aph(2'')-Ia* genes mediate resistance to aminoglycosides.[178] The principal genetic mechanism of fusidic acid resistance is the harboring of the *fusC* or *fusA* mutations.[179,180] The *fusC* gene renders approximately 99% of the *S. aureus* ST1 isolates resistant to fusidic acid.[181]

*Acinetobacter spp.* in sebum-rich environments may exert toxic and proinflammatory effects on keratinocytes, which can also influence AD symptoms. Compared to *Staphylococcus epidermidis*, *P. acnes* exhibits a more stable genome and fewer antibiotic resistance genes and virulence factors.[182]

Wang et al. compared the *S. aureus* genome of AD patients and healthy individuals. They found that lantibiotic genes, glycopeptide transporter genes, and *AMR* genes were more active in the AD group, conferring resistance to lantibiotics, glycopeptides, macrolides, aminoglycosides, streptozotocin, and methicillin antibiotics, respectively.[183] Future research should explore ARG-AD interactions in order to develop targeted antimicrobial strategies.

### Nanoparticle

Nanoparticles, including silicon dioxide and titanium dioxide (TiO2), are increasingly investigated as drug carriers but may also exacerbate AD.[184-186] Across most studies, nanoparticles have been shown toenhance drug diffusion and bioavailability with great potential for drug targeting.[187] Silicon dioxide and titanium dioxide are widely used and generally regarded as biologically inert. However, Hirai et al. reported that, relative to injection of Dermatophagoides pteronyssinus (Dp) alone, co-administration of amorphous silica nanoparticles (SPs) with Dp induced exacerbation of AD in mice. Moreover, smaller SPs were associated with more pronounced exacerbation. These effects may be attributable to the induction of IL-18 and TSLP. SPs induce excessive induction of total IgE and a more intense systemic Th2 response.[188] When the skin barrier is compromised, exposure to TiO(2) nanoparticles can result in excessive IL-4 production, elevated serum levels of total IgE and histamine, and exacerbated Th2-related immune responses.[189]

### Aluminum

Aluminum salts (AS) are now among the most commonly used adjuvants in human vaccines.[190] Studies have shown that high doses of AS injection may suppress Th1 and Th17 responses and promote the differentiation of CD4 T cells into Th2 effector cells via skin inflammation driven by type 2 immune responses.[191,192]

Aluminum is also occasionally used as a precipitant in antigen extraction. Netterlid et al. investigated the development of contact aluminum allergy during allergen-specific immunotherapy and found that children and individuals with AD accounted for a higher proportion of those who developed aluminum allergy.[193]

### Micro and nanoplastics

Microplastics and nanoplastics are lightweight and small-sized particles, which can easily penetrate into natural habitats and rivers and enter the food chain.[194,195] Nanoplastics can induce apoptosis via the mitochondrial apoptotic pathway, induce oxidative stress, and potentially disrupt skin barrier dysfunction.[196-201] Nonetheless, the specific mechanisms underlying the effects of microplastics and nanoplastics on AD remain to be fully elucidated.

## CONCLUSION

### Epidemiology and mechanisms

Numerous ECs may increase the prevalence of AD, whereas certain ECs exhibit immunosuppressive properties that attenuate AD symptoms. The effects of some ECs on AD are sex-related (Table 4). ECs influence AD through a variety of underlying mechanisms (Figure 4), including disruption of immune homeostasis and the promotion of oxidative stress.

### Clinical significance

Among ECs associated with increased AD prevalence, their relationships

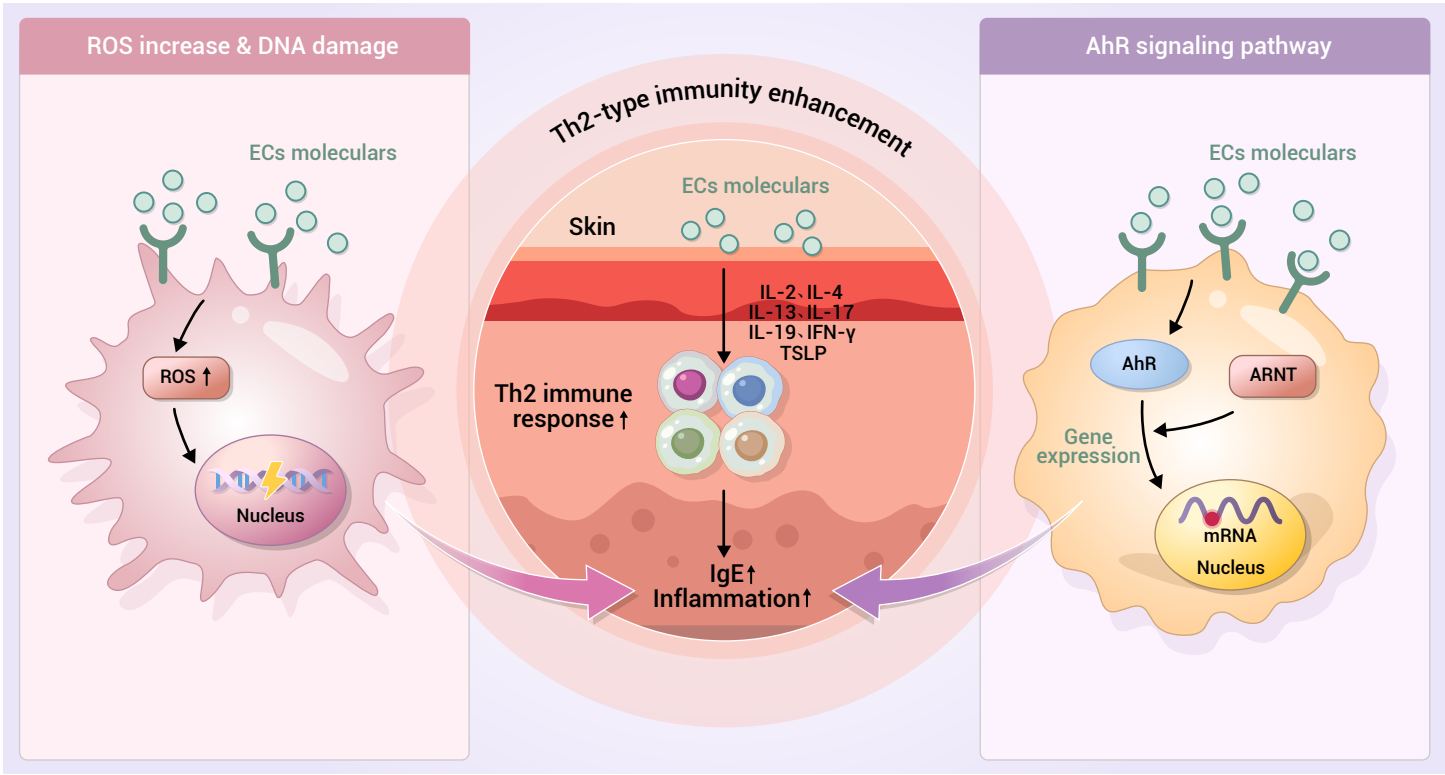


**Figure 4. Major pathways by which ECs affect AD** Three major pathways are implicated: Th2-type immunity enhancement, ROS increase and DNA damage, and the AhR signaling pathway[53,64,78,101]. ROS, reactive oxygen species; TSLP, thymic stromal lymphopoietin; AhR, aryl hydrocarbon receptor; ARNT, AHR nuclear translocator.

with IgE level vary considerably. This variability may reflect different AD endotypes, suggesting that precision medicine approaches may yield better treatment outcomes. Evaluation of occupational and lifestyle factors may help assess ECs exposure history in AD patients, thereby optimizing treatment plans and informing lifestyle recommendations. For example, reducing maternal consumption of ultra-processed foods may lower the risk of infantile AD.[202]

## Future perspectives

Emerging pollutants, such as nanoparticles, ARGs, and microplastics, present greater research potential than traditional pollutants, owing to their rising environmental concentrations and the persistent knowledge gaps surrounding their biological effects. In addition, certain substances previously presumed to be innocuous may, in fact, exert harmful effects. Future research may therefore need to re-evaluate the impact of commonly encountered substances in our lives and their combined effects on AD. Given that most contaminants occur as mixtures, both in vitro and in vivo, the combined effects of numerous ECs represent another promising research direction. A typical example is that some ECs may impair the skin barrier, thereby increasing the absorption of other contaminants.

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## AUTHOR CONTRIBUTIONS

MS, JS, XC and YX contributed to the development of the study concept and design. LH, YZ summarized literature, conducted research analyses. LH, YZ, HX, YL, ZZ, and ZX wrote the draft of the review. YT, KH, MS, JS, XC and YX provided critical revision of the manuscript. SW contributed to the revision of the manuscript. All authors contributed to and approved the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## DATA AND CODE AVAILABILITY

This review does not report original data and code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request (xiaoyixy@csu.edu.cn).