Asthma and Environmental Exposures to Phenols, Polycyclic Aromatic Hydrocarbons, and Phthalates in Children

Medina S. Jackson-Browne[1,2], **Marisa A. Patti**[3], **Noelle B. Henderson**[4], **Marissa Hauptman**[1,2,5], **Wanda Phipatanakul**[2,6]

[1]Division of General Pediatrics, Boston Children's Hospital, Member of the Faculty, Harvard Medical School, 300 Longwood Avenue, LM 7605.1, Boston, MA 02115, USA

[2]Harvard Medical School, Harvard University, Boston, MA, USA

[3]AJ Drexel Autism Institute, Drexel University, Philadelphia, PA, USA

[4]Department of Environmental Health, Boston University School of Public Health, Boston University, Boston, MA, USA

[5]New England Pediatric Environmental Health Specialty Unit, Boston, MA, USA

[6]Division of Allergy and Immunology, Boston Children's Hospital, Boston, MA, USA

Introduction

The incidence and prevalence of childhood asthma and other allergic diseases has increased greatly over the past few decades [1]. A common biological pathway to asthma in children is often referred to as the "atopic march," characterized by the development of early life atopic dermatitis (eczema) and allergic sensitization (atopy), which leads to allergic rhinitis and asthma in childhood. For example, children with early onset eczema (diagnosed prior to 2 years of age) have 3.71 times the odds of developing allergic rhinitis and 3.80 times the odds of developing asthma by age 4 [2]. A variety of risk factors have been implicated in the development of allergic diseases, including environmental factors like increased exposure to endocrine disrupting chemicals (EDCs) and decreased microbial exposure during gestation and early life [1, 3–6]. During the prenatal and early childhood periods, the fetus and child may be particularly vulnerable to the effects of EDCs due to immature detoxification pathways and rapid growth and development [7–9]. For instance, the PON1 enzyme is critical to detoxification and mitigation of oxidative stress but is not fully developed until the age of 9 [10]. Further, alterations to typical hormonal function may lead to hyperactivity of immune responses, such as increased promotion of type 2 helper T cells (Th2), where Th2 responses have been reported in allergy-related outcomes [11].

✉Medina S. Jackson-Browne, medina.jackson-browne@childrens.harvard.edu.

The burden of asthma and allergic diseases is not evenly distributed; a higher prevalence of asthma and eczema is observed among Black and Hispanic populations and in urban areas, particularly in poorer neighborhoods [12–14]. Specifically, the prevalence of asthma among non-Hispanic white children is 8.2% versus 21.2% for Puerto Rican children and 14.5% for non-Hispanic Black children [15]. One study found the incidence of asthma at age 4 years to be 0.25 times higher among Black children with no family history of asthma compared to white children [16]. The disparities observed in the disproportionate burden of asthma and allergic disease by race and socioeconomic status (SES) are in part due to selected indoor allergens [17], secondhand smoke, exposure to outdoor air pollution, and maternal prenatal stress [18]. However, it is believed that associations between race and exposure to indoor allergens may be explained by residual confounding due to characteristics of their housing [19]. Air quality is an important factor for respiratory diseases and increased exposure to $PM_{2.5}$ has been associated with childhood asthma incidence [20]. This impact is not evenly distributed, and exposure to air pollution and $PM_{2.5}$ varies by race [21]. Given the disproportionate burden of exposure, the negative health impacts of asthma and allergic disease are similarly disproportionate. Asthma and allergic conditions are chronic and can impact multiple aspects of a child's life and daily functioning, including their ability to go to school. Children with asthma experience more school absenteeism compared to their non-asthmatic peers, which place an additional burden on these children [22]. Additionally, it is hypothesized that asthma-related school absences are attributable to disrupted and thus reduced sleep [23].

In previous work, we discussed two potential pathways that early life antimicrobial (including triclosan and paraben) exposure could adversely affect immune development, contributing to increased risk of immune-mediated diseases, such as asthma, in children [24••]. First, decreased exposure to microbes, due to antimicrobial use, during pregnancy and in early childhood can alter the priming of immune systems in infants, increasing the risk of allergic disease development. Second, direct exposure of antimicrobial compounds through oral and dermal routes can alter the microflora on the lung, gut, and/or skin, inducing a hypersensitive reactive state of immune system receptors in these organs, thus increasing the risk for hypersensitivity diseases such as eczema and asthma [24].

Given the novel methods of applying mixture approaches to evaluating the impacts of multiple chemical exposures on child health outcomes, limited evidence has considered the impacts of chemical mixtures of total and individual chemical classes on child asthma-related outcomes. Important questions remain as to the causative relationship of these chemicals, individually and collectively, with asthma development in children [24••, 25•, 26•]. In this review, we aimed to evaluate the impact that additional environmental chemical exposures with EDC properties, individually and collectively, have on asthma and allergy-related health outcomes among children. Our main objective is to discuss findings from primary epidemiological literature measuring the associations between urinary biomarkers of phenols, phthalates, and polycyclic aromatic hydrocarbons and their mixtures with asthma-related health outcomes (e.g., asthma symptoms and allergic sensitization) in children.

We identified toxicological and primary epidemiological studies of phenols, phthalates, polycyclic aromatic hydrocarbons, and their mixtures with asthma and allergic disease-related outcomes in children. In an update to a prior review, we used Google Scholar and PubMed to identify manuscripts published since 2019 [24].

Importance of Investigating Environmental Mixtures in Epidemiological Studies

The importance of examining chemical mixtures, in addition to individual compounds, to identify environmental determinants of diseases is increasingly recognized in environmental epidemiology studies [27]. The main limitation to evaluating chemical mixtures is the high correlation patterns seen between different compounds which may amplify measurement error and bias in traditional regression analyses [28, 29••]. One such analytical tool to address these limitations is weighted quantile sum (WQS) regression [28, 30••, 31••], an approach that is particularly well suited to identify individual components of a mixture that are driving the association in the presence of multiple co-exposures [32•]. Across classes of exposure to EDCs, metals, and air pollutants, there is evidence that individual chemicals, as well as their mixtures, have been associated with adverse childhood health including asthma and neurodevelopmental outcomes [33, 34]. As methods to evaluate complex and highly correlated chemicals evolve, utilizing mixtures approaches can adequately capture the multidimensional nature of these exposures, and thus shed light on how co-exposure to multiple chemicals contributes to child health outcomes. This is an improvement on traditional statistical approaches that historically have utilized a single chemical at a time approach.

In a pilot study [not yet published], we found high correlations between different EDCs measured from urine samples of school-aged children, predominantly of children with minority race and ethnicity [35]. Similar patterns of results were observed among other environmental exposure studies of chemical mixtures [29, 36–39,]. We utilized the WQS regression method to evaluate associations between phenols, parabens, PAHs (polycyclic aromatic hydrocarbons), and phthalates measured from stored urine samples in pregnancy and early childhood collected in 2016 to evaluate associations between chemical mixtures and asthma related outcomes. In short, WQS regression was used to test for a mixture effect of chemicals on the outcome while accommodating for a complex correlation pattern among the chemical components. When the WQS index is statistically significant it identifies important chemicals in a mixture of correlated environmental chemicals [32•]. Additional methods for assessing exposure to chemical mixtures are rapidly developing and include Bayesian kernel machine regression (BKMR), quantile-based G-computation (QGComp), principal component analysis (PCA) among others [29, 30••, 31••].

Results of Recent Studies

Triclosan and Paraben Exposures and Asthma-Related Health Outcomes

Triclosan is an artificial antimicrobial chemical and prior to its phase out in 2017, it was added to personal care products including toothpaste and hand soap [40, 41]. Thus, the primary exposure routes for humans are dermal and oral [42]. Triclosan is non-persistent and is typically excreted from the body in less than 24 h, though individuals that have

been exposed daily due to the episodic nature of exposure related behaviors (i.e., daily teeth brushing) may have low levels of constant exposure [43]. Exposure to triclosan is wide-spread with as much as 75% of the US population, including pregnant individuals, has detectable levels of triclosan in urine [44, 45].

We previously summarized epidemiologic findings of triclosan and paraben exposures and asthma/eczema risks in children from studies conducted between 2015 and 2019 [24••]. We observed associations with childhood levels of triclosan with asthma- and allergy-related outcomes in children but not prenatal levels, consistent with conclusions drawn from a more recent meta-analysis [46]. From the time of our last review, more recent work has reported that childhood levels of TCS were associated with elevated serum IgE levels in childhood, as well as subsequent diagnosis of asthma and atopic dermatitis [47]. In studies evaluating the impact of triclosan on asthma outcomes in children, urinary triclosan concentrations were associated with increased odds of asthma [48–50] and sex-specific effects in boys only [51], though these results were not consistently found in all studies [25, 52, 53,]. A review of the toxicology of triclosan highlighted antibiotic resistance, skin irritations, hormone homeostasis disruption, and increasing rates of allergic disease conditions as potential health risks associated with triclosan exposure [40]. Conversely, another review, including studies prior to 2009, of the health effects of triclosan exposure found no conclusive evidence of adverse health effects of triclosan exposure in children or adults [42]. However, in response to epidemiologic and toxicological reports, the Food and Drug Administration (FDA) of the USA issued a final ruling in 2016 that triclosan could no longer be used in over-the-counter consumer antiseptic products as of September 2017 [54]. Triclosan has since been replaced with benzalkonium chloride (BAC), benzethonium chloride (BEC) or chloroxylenol (CX), in antibacterial products [31]. These compounds were originally developed for use in medications and had been deemed safe at product-specific levels, though the safety of these chemicals at elevated doses, as they exist in personal care products, has not yet been studied in humans, though animal models suggest they may be as toxic, if not more so than triclosan [55]. However, during the COVID-19 pandemic, exposure to triclosan increased due to the emphasis on hygiene and prevention of disease spread [56]. Although many of these studies were published after the FDA ruling, the urine samples analyzed for triclosan in these studies were collected prior to 2016 [57, 58•, 59•, 60]. According to NHANES data from 2005 to 2016, the average urinary triclosan levels were steadily decreasing before this ruling [61]. We were unable to identify any additional epidemiological studies in US populations conducted with urine samples collected after the 2016 government ruling.

Parabens are primarily used in pharmaceuticals, foods, cosmetics, and personal care products for their antimicrobial properties, with exposure generally occurring through dermal or oral absorption [62–64]. While parabens have short half-lives (~ 2–3 h), exposure is ubiquitous among adults and children in the USA [44]. However, biomonitoring studies reported differential urinary concentrations of parabens, such that median concentrations tend to be higher among women and those who identify as non-Hispanic Black [64, 65]. In fact, one cohort study found a dose-response relationship between increasing urinary concentrations of parabens with frequency of personal care product use and subsequent biomarkers of exposure to be higher in women relative to men [66]. Prior observational studies have identified inconsistent associations between childhood paraben

exposure and allergic outcomes. For example, cross-sectional analyses identified a positive association between urinary methyl and propyl paraben concentrations with increased odds of aeroallergen sensitization and asthma in children [48], while other cohort studies report no associations between parabens with asthma, allergen sensitization, or other inflammatory biomarkers [51–53, 67•, 68]. However, these inconsistencies may be explained by child sex, where boys may be more susceptible compared to girls [26, 51, 53].

Additional Phenol Exposures and Asthma-Related Health Outcomes

Phenols are used in a variety of consumer products ranging from sunscreen (benzophenone-3, BP3) [69], deodorizers (2,5-dichlorophenol [2,5-DCP]) [70], preservatives (2.4-dichlorophenol [2,4-DCP]) [71], food packaging (Bisphenol A) [72], and as an antimicrobial in personal care products (triclosan, parabens) [44, 69, 73].

While these chemicals are considered to be non-persistent, exposure tends to be continual due to habitual use of phenol-containing products, and emerging evidence suggests they may deposit in human adipose tissue [74]. It is also important to mention that many phenols, such as BPA are being replaced with chemicals such as bisphenol S (BPS) and bisphenol F (BPF), and ongoing toxicology information is needed [75]. Cross-sectional analyses using NHANES data found urinary concentrations of BPF and BPS, replacement chemicals of BPA, are associated with asthma in participants aged 12 years and greater [76]. Previous reports suggest phenols may confer allergy and asthma-related risks in children as well as adults [24••]. Specifically, positive associations were observed between BPS and asthma among women, but not men [66]. Prior work suggests an inverse association between prenatal urinary concentrations of 2,5-DCP with eczema and allergy outcomes in boys only [25], while others report prenatal BPA to be associated with risk of childhood wheeze and asthma outcomes [77]. In particular, childhood BPA exposure in low-income, minority cohort, was associated with asthma morbidity in children where boys were at an increased odds of asthma symptom days and health care utilization due to asthma-related concerns compared to girls [78].

Polycyclic Aromatic Hydrocarbon and Phthalate Exposures and Asthma-Related Health Outcomes

Polycyclic aromatic hydrocarbons (PAHs) are the result of incomplete combustion of organic materials included fossil fuels (i.e., coal), wood, and tobacco, exposing individuals primarily through inhalation [79, 80]. Several studies reported that increased exposure to PAHs was associated with asthma outcomes in children [81–85], while others report null fundings [79, 80, 86]. Unlike the other chemicals evaluated here, women may be more susceptible to the adverse effects of PAHs than men, due to sex-specific differences in the metabolism of PAHs and resulting oxidative stress, though this has not been evaluated in children [87, 88].

Phthalates are plasticizers commonly used in medical supplies, food packaging, and personal care products [89, 90]. Individual phthalates have been previously identified with wheeze and asthma in children [9, 67, 91], though results are inconsistent across studies [9, 25•, 67•, 91–93], with some reporting sex-specific effects where boys are more affected than

girls [25]. Phthalates are EDCs, and sex-specific immune responses to hormone disruption may explain the observed sex-specific differential effects, underlying pathways in asthma development in boys versus girls [94, 95]. Some studies did consider the combined effects of phthalates by considering the impact of phthalate specific chemical class mixtures on child respiratory outcomes [37, 96]. One study evaluated the impact of gestational phthalate mixtures with childhood asthma and wheeze outcomes and found that the adverse effects of phthalate mixtures on respiratory outcomes were only present in boys, but not within girls or within the entire study sample [37], and another found that childhood mixtures of phthalate metabolites was associated with wheeze and eczema in children aged 7 years [96].

Synthesis of Existing Evidence (Table 1)

Research Gaps and Future Directions—Given the influx and development of higher dimensional statistical techniques, there are increasing efforts to quantify simultaneous co-exposures to chemical mixtures. However, few efforts have been made to compare the composition of chemical mixtures across demographic characteristics including race/ethnicity, socioeconomic position, and biological sex. It is standard in the literature to assess chemical concentrations by these factors; however, it has yet to catch on for the individual components of mixture analyses. Future work should include stratified analyses by child sex and race/ethnicity (as a proxy for racism). For instance, boys have been found to be at increased susceptibility to EDC exposure relative to girls due to anti-androgenic and estrogenic effects [97]. Stratification by race in future studies is necessary as current work suggests that Black children, specifically boys, are at increased risk of asthma and other allergy-related outcomes relative to EDC exposure [98]. Given that race is a social construct and not a biological variable, we speculate these differences can be attributed to structural racism leading to lack of access to healthy housing, segregation, and increased use of personal care products marketed to promote Eurocentric beauty standards [99]. For example, an intervention study found that children and their families who moved to neighborhoods with lower rates of poverty showed reduced childhood asthma morbidity, suggesting that housing discrimination can exacerbate asthma symptoms [100]. As such, it is crucial for researchers to assess chemical mixture compositions across demographic factors as they identify strategies to minimize and mitigate exposure to EDCs, particularly among populations vulnerable to exposure.

Conclusions

We reviewed existing evidence for the association of chemical mixtures or individual urinary metabolites of phenol, paraben, polycyclic aromatic hydrocarbons, and phthalate analytes with asthma- and allergy-related health outcomes in children. Among studies that pool all children, there is inconsistent evidence in support of associations between chemical mixtures with asthma and allergy outcomes; however, in studies that included stratified analyses, results suggest that age and biological sex may modify associations between these chemical mixtures and asthma and allergy outcomes. Although Black and Hispanic children are at a higher risk for asthma morbidity, many studies lack the power to detect differences by race and/or ethnicity given the small number of minorities included in their studies. Future work should evaluate the ongoing impact of chemical mixtures on asthma- and allergy-related

health outcomes in minority children, and the impact of environmental interventions on reducing asthma-related outcomes in children over time.

Funding

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006;355(21):2226–35. [PubMed: 17124020]

2. Chiu C-Y, et al. Early-onset eczema is associated with increased milk sensitization and risk of rhinitis and asthma in early childhood. J Microbiol Immunol Infect. 2020;53(6):1008–13. [PubMed: 31129013]

3. Martinez FD, Vercelli D. Asthma. Lancet. 2013;382(9901):1360–72. [PubMed: 24041942]

4. Antó JM. Recent advances in the epidemiologic investigation of risk factors for asthma: a review of the 2011 literature. Curr Allergy Asthma Rep. 2012;12(3):192–200. [PubMed: 22422360]

5. Hartmann EM, et al. Antimicrobial chemicals are associated with elevated antibiotic resistance genes in the indoor dust microbiome. Environ Sci Technol. 2016;50(18):9807–15. [PubMed: 27599587]

6. Bertelsen RJ, et al. Triclosan exposure and allergic sensitization in Norwegian children. Allergy. 2013;68(1):84–91. [PubMed: 23146048]

7. Spanier AJ, et al. Prenatal exposure to bisphenol A and child wheeze from birth to 3 years of age. Environ Health Perspect. 2012;120(6):916–20. [PubMed: 22334053]

8. Factor-Litvak P, et al. Persistent associations between maternal prenatal exposure to phthalates on child IQ at age 7 years. PLoS ONE. 2014;9(12):e114003. [PubMed: 25493564]

9. Whyatt RM, et al. Prenatal phthalate and early childhood bisphenol A exposures increase asthma risk in inner-city children. J Allergy Clin Immunol. 2014;134(5):1195–1197.e2. [PubMed: 25174861]

10. Schug TT, et al. Endocrine disrupting chemicals and disease susceptibility. J Steroid Biochem Mol Biol. 2011;127(3-5):204–15. [PubMed: 21899826]

11. Yang SN, et al. The effects of environmental toxins on allergic inflammation. Allergy Asthma Immunol Res. 2014;6(6):478–84. [PubMed: 25374746]

12. Togias A, et al. Asthma in the inner city: the perspective of the National Institute of Allergy and Infectious Diseases. J Allergy Clin Immunol. 2010;125(3):540–4. [PubMed: 20226290]

13. Shaw TE, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011;131(1):67–73. [PubMed: 20739951]

14. Akinbami L. The state of childhood asthma, United States, 1980-2005. Adv Data. 2006;381:1–24.

15. Perez MF, Coutinho MT. An overview of health disparities in asthma. Yale J Biol Med. 2021;94(3):497–507. [PubMed: 34602887]

16. Johnson CC, et al. US childhood asthma incidence rate patterns from the ECHO Consortium to identify high-risk groups for primary prevention. JAMA Pediatr. 2021;175(9):919–27. [PubMed: 33999100]

17. Celedón JC, et al. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. J Allergy Clin Immunol. 2007;120(1):144–9. [PubMed: 17507083]

18. Bose S, et al. Prenatal nitrate exposure and childhood asthma. Influence of maternal prenatal stress and fetal sex. Am J Respir Crit Care Med. 2017;196(11):1396–403. [PubMed: 28661182]

19. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. Curr Opin Allergy Clin Immunol. 2009;9(2):154–60. [PubMed: 19326508]

20. Garcia E, et al. Association of changes in air quality with incident asthma in children in California, 1993-2014. JAMA. 2019;321(19):1906–15. [PubMed: 31112259]

21. Liu J, et al. Disparities in air pollution exposure in the United States by race/ethnicity and income, 1990-2010. Environ Health Perspect. 2021;129(12):127005. [PubMed: 34908495]

22. Moonie SA, et al. Asthma status and severity affects missed school days. J Sch Health. 2006;76(1):18–24. [PubMed: 16457681]

23. Daniel LC, et al. Missed sleep and asthma morbidity in urban children. Ann Allergy Asthma Immunol. 2012;109(1):41–6. [PubMed: 22727156]

24••. Jackson-Browne MS, et al. , The impact of early-life exposure to antimicrobials on asthma and eczema risk in children. Curr environ health rep., 2019. 6(4):214–224. [PubMed: 31745828] This is our prior review of phenol exposure and asthma risk in children.

25•. Buckley JP, et al. Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years. Environ Int. 2018;115:79–88. [PubMed: 29550712] This paper shows evidence that child sex modifies associations between prenatal triclosan concentrations and asthma and eczema.

26•. Quirós-Alcalá L, et al. Paraben exposures and asthma-related outcomes among children from the US general population. J Allergy Clin Immunol. 2019;143(3):948–956.e4. [PubMed: 30194988] This paper shows evidence that paraben concentrations were associated with increased emergency department visits among asthmatic boys.

27••. Braun JM, et al. What can epidemiological studies tell us about the impact of chemical mixtures on human health? Environ Health Perspect. 2016;124(1):A6–9. [PubMed: 26720830] This paper summarizes the benefits of evaluating chemical mixture exposures in epidemiological studies.

28••. Hamra GB, Buckley JP. Environmental exposure mixtures: questions and methods to address them. Curr epidemiol rep. 2018;5(2):160–5. [PubMed: 30643709] This paper reviews different methods for measuring chemical mixture exposures.

29••. Gibson EA, Goldsmith J, Kioumourtzoglou M-A. Complex mixtures, complex analyses: an emphasis on interpretable results. Curr environ health rep. 2019;6(2):53–61. [PubMed: 31069725] This paper explains the complexities of analyzing chemical mixtures in epidemiological studies.

30••. Stafoggia M, et al. Statistical approaches to address multipollutant mixtures and multiple exposures: the state of the science. Curr Environ Health Rep. 2017;4(4):481–90. [PubMed: 28988291] This paper describes the statistical complexities of measuring chemical mixtures in epidemiology studies.

31••. Lazarevic N, et al. Statistical methodology in studies of prenatal exposure to mixtures of endocrine-disrupting chemicals: a review of existing approaches and new alternatives. Environ Health Perspect. 2019;127(2):26001–1. [PubMed: 30720337] This paper describes the statistical complexities of measuring chemical mixtures in epidemiology studies.

32•. Carrico C, et al. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J Agric Biol Environ Stat. 2015;20(1):100–20. [PubMed: 30505142] This paper describes how to analyze highly correlated data.

33. Reddam A, et al. Air pollution and human endogenous retrovirus methylation in the school inner-city asthma intervention study. Toxicol Sci. 2023;193(2):166–74. [PubMed: 37042721]

34. Chiu YM, et al. Prenatal ambient air pollutant mixture exposure and neurodevelopment in urban children in the Northeastern United States. Environ Res. 2023;233:116394. [PubMed: 37315758]

35•. Phipatanakul W, et al. The school inner-city asthma intervention study: design, rationale, methods, and lessons learned. Contemp Clin Trials. 2017;60:14–23. [PubMed: 28619649] This paper describes the study design of a school-based asthma intervention trial.

36•. Kalloo G, et al. Exposures to chemical mixtures during pregnancy and neonatal outcomes: the HOME study. Environ Int. 2020;134:105219. [PubMed: 31726361] This paper utilizes a statistical method for measuring chemical mixtures.

37. Adgent MA, et al. A combined cohort analysis of prenatal exposure to phthalate mixtures and childhood asthma. Environ Int. 2020;143:105970–0. [PubMed: 32763629]

38•. Berger K, et al. Prenatal phthalate, paraben, and phenol exposure and childhood allergic and respiratory outcomes: evaluating exposure to chemical mixtures. Sci Total Environ. 2020;725:138418–8. [PubMed: 32302842] This paper utilizes a statistical method for measuring chemical mixtures and asthma in childen.

39. Tang N, et al. Maternal bisphenol A and triclosan exposure and allergic diseases in childhood: a meta-analysis of cohort studies. Environ Sci Pollut Res Int. 2022;29(55):83389–403. [PubMed: 35764729]

40. Dann AB, Hontela A. Triclosan: environmental exposure, toxicity and mechanisms of action. J Appl Toxicol. 2010;31(4):285–311.

41. Geer LA, et al. Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in Brooklyn New York. J Hazard Mater. 2017;323(Pt A):177–83. [PubMed: 27156397]

42. Rodricks JV, et al. Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Crit Rev Toxicol. 2010;40(5):422–84. [PubMed: 20377306]

43. Sandborgh-Englund G, et al. Pharmacokinetics of triclosan following oral ingestion in humans. J Toxicol Environ Health A. 2006;69(20):1861–73. [PubMed: 16952905]

44. Calafat AM, et al. Urinary concentrations of four parabens in the U.S. population: NHANES 2005-2006. Environ Health Perspect. 2010;118(5):679–85. [PubMed: 20056562]

45. Arbuckle TE, et al. Exposure to free and conjugated forms of bisphenol A and triclosan among pregnant women in the MIREC cohort. Environ Health Perspect. 2015;123(4):277–84. [PubMed: 25494523]

46. Manzano-Salgado CB, et al. Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort. Environ Int. 2017;108:278–84. [PubMed: 28917208]

47. Lin MH, et al. Effect of triclosan on the pathogenesis of allergic diseases among children. J Expo. Sci Environ Epidemiol 2022;32(1):60–8. [PubMed: 33654271]

48. Spanier AJ, et al. The associations of triclosan and paraben exposure with allergen sensitization and wheeze in children. Allergy Asthma Proc. 2014;35(6):475–81. [PubMed: 25584915]

49. Savage JH, et al. Urinary triclosan levels and recent asthma exacerbations. Ann Aller Asthma Immunol. 2014;112(2):179–181.e2.

50. Berger K, et al. Associations between prenatal maternal urinary concentrations of personal care product chemical biomarkers and childhood respiratory and allergic outcomes in the CHAMACOS study. Environ Int. 2018;121(Pt 1):538–49. [PubMed: 30293015]

51. Lee-Sarwar K, et al. Prenatal and early-life triclosan and paraben exposure and allergic outcomes. J. Allergy Clin. Immunol 2018;142(1):269–278.e15. [PubMed: 29111213]

52. Mitsui-Iwama M, et al. Exposure to paraben and triclosan and allergic diseases in Tokyo: a pilot cross-sectional study. Asia Pac Allergy. 2019;9(1):e5–5. [PubMed: 30740353]

53. Vernet C, et al. In utero exposure to select phenols and phthalates and respiratory health in five-year-old boys: a prospective study. Environ Health Perspect. 2017;125(9):097006–6. [PubMed: 28934727]

54•. Food and Drug Administration, H., Safety and effectiveness of consumer antiseptics; topical antimicrobial drug products for over-the-counter human use. Final rule., F.a.D. Administration, Editor. 2016, HHS: Federal Register.FDA rule for discontinued use of triclosan in consumer products.

55. Sreevidya VS, et al. Benzalkonium chloride, benzethonium chloride, and chloroxylenol - three replacement antimicrobials are more toxic than triclosan and triclocarban in two model organisms. Environ Pollut. 2018;235:814–24. [PubMed: 29348075]

56. Usman M, Farooq M, Hanna K. Environmental side effects of the injudicious use of antimicrobials in the era of COVID-19. Sci Total Environ. 2020;745:141053. [PubMed: 32702547]

57. Mínguez-Alarcón L, et al. Pregnancy urinary concentrations of bisphenol A, parabens and other phenols in relation to serum levels of lipid biomarkers: Results from the EARTH study. Sci Total Environ. 2022;833:155191–1. [PubMed: 35421480]

58•. Hu P, et al. Associations between exposure to a mixture of phenols, parabens, and phthalates and sex steroid hormones in children 6–19 years from NHANES, 2013–2016. Sci Total Environ. 2022;822:153548. [PubMed: 35114227] This paper utilizes a statistical method for measuring chemical mixtures and sex hormones in childen.

59•. Zhang Y, et al. Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity: comparison of three statistical models. Environ Int. 2019;123:325–36. [PubMed: 30557812] This paper compares 3 statistical methods for measuring chemical mixtures.

60. Patti MA, et al. Gestational triclosan exposure and infant birth weight: a systematic review and meta-analysis. Environ Int. 2021;157:106854–4. [PubMed: 34560323]

61. Li R, et al. Temporal trends in risk of bisphenol A, benzophenone-3 and triclosan exposure among U.S. children and adolescents aged 6–19 years: findings from the National Health and Nutrition Examination Survey 2005–2016. Environ Res. 2023;216:114474. [PubMed: 36202243]

62. Nowak K, Jabło ska E, Ratajczak-Wrona W. Immunomodulatory effects of synthetic endocrine disrupting chemicals on the development and functions of human immune cells. Environ Int. 2019;125:350–64. [PubMed: 30743143]

63. Larsson K, et al. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. Environ Int. 2014;73:323–33. [PubMed: 25216151]

64. Food and Drug Administration, H., Parabens in Cosmetics, F.a.D. Administration, Editor. 2022, HHS.

65. Chan M, et al. Racial/ethnic disparities in pregnancy and prenatal exposure to endocrine-disrupting chemicals commonly used in personal care products. Curr Environ Health Rep. 2021;8(2):98–112. [PubMed: 34046860]

66. Vindenes HK, et al. Exposure to environmental phenols and parabens, and relation to body mass index, eczema and respiratory outcomes in the Norwegian RHINESSA study. Environ health : a global access sci source. 2021;20(1):81–1.

67•. Berger K, et al. Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric aller immunol: official public Europ Soc Pediatr Allergy Immunol. 2019;30(1):36–46.This paper shows evidence that phthalate concentrations were associated with elevated immune biomarkers and respiratory measures in children.

68. Aung MT, et al. , Corrigendum to "Associations between maternal plasma measurements of inflammatory markers and urinary levels of phenols and parabens during pregnancy: A repeated measures study" [Sci. Total Environ. 650 (Pt 1) (2019) 1131–1140]. Sci. Total Environ, 2019. 658: p. 1640. [PubMed: 30616924]

69. Calafat AM, et al. Concentrations of the sunscreen agent benzophenone-3 in residents of the United States: National Health and Nutrition Examination Survey 2003--2004. Environ Health Perspect. 2008;116(7):893–7. [PubMed: 18629311]

70. Harley KG, et al. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. Hum Reprod. 2019;34(1):109–17. [PubMed: 30517665]

71. Liao C, Kannan K. A Survey of alkylphenols, bisphenols, and triclosan in personal care products from China and the United States. Arch Environ Contam Toxicol. 2014;67(1):50–9. [PubMed: 24639116]

72. Rogers JA, Metz L, Yong VW. Review: Endocrine disrupting chemicals and immune responses: a focus on bisphenol-A and its potential mechanisms. Mol Immunol. 2013;53(4):421–30. [PubMed: 23123408]

73. Ferguson KK, et al. Personal care product use among adults in NHANES: associations between urinary phthalate metabolites and phenols and use of mouthwash and sunscreen. J Expo Sci Environ Epidemiol. 2017;27(3):326–32. [PubMed: 27168391]

74. Artacho-Cordón F, et al. Assumed non-persistent environmental chemicals in human adipose tissue; matrix stability and correlation with levels measured in urine and serum. Environ Res. 2017;156:120–7. [PubMed: 28342347]

75. Wu L-H, et al. Occurrence of bisphenol S in the environment and implications for human exposure: a short review. Sci Total Environ. 2018;615:87–98. [PubMed: 28963899]

76•. Mendy A, et al. Association of urinary levels of bisphenols F and S used as bisphenol A substitutes with asthma and hay fever outcomes. Environ Res. 2020;183:108944–4. [PubMed: 31911000] The paper measures associations between bisphenolA substitutes with asthma and allergy outcomes.

77. Xie M-Y, et al. Exposure to bisphenol A and the development of asthma: a systematic review of cohort studies. Reprod Toxicol. 2016;65:224–9. [PubMed: 27542534]

78•. Quirós-Alcalá L, et al. Exposure to bisphenols and asthma morbidity among low-income urban children with asthma. J Allergy Clin Immunol. 2021;147(2):577–586.e7. [PubMed: 32736870] The paper measures associations between bisphenolA substitutes with asthma-related health outcomes in children.

79. Rosa MJ, et al. Prenatal exposure to polycyclic aromatic hydrocarbons, environmental tobacco smoke and asthma. Respir Med. 2011;105(6):869–76. [PubMed: 21163637]

80. Jung KH, et al. Polycyclic aromatic hydrocarbon exposure, obesity and childhood asthma in an urban cohort. Environ Res. 2014;128:35–41. [PubMed: 24407477]

81. Gale SL, et al. Polycyclic aromatic hydrocarbon exposure and wheeze in a cohort of children with asthma in Fresno, CA. J Exposure Sci Environ Epidemiol. 2012;22(4):386–92.

82. Jung KH, et al. Repeated exposure to polycyclic aromatic hydrocarbons and asthma: effect of seroatopy. Ann Allergy Asthma Immunol. 2012;109(4):249–54. [PubMed: 23010230]

83. Jung KH, et al. Repeatedly high polycyclic aromatic hydrocarbon exposure and cockroach sensitization among inner-city children. Environ Res. 2015;140:649–56. [PubMed: 26073203]

84. Wang IJ, Karmaus WJJ, Yang C-C. Polycyclic aromatic hydrocarbons exposure, oxidative stress, and asthma in children. Int Arch Occup Environ Health. 2017;90(3):297–303. [PubMed: 28175985]

85. Hsu S-C, et al. Differential time-lag effects of ambient PM2.5 and PM2.5-bound PAHs on asthma emergency department visits. Environ Sci Pollut Res. 2020;27(34):43117–24.

86. Miller RL, et al. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. Chest. 2004;126(4):1071–8. [PubMed: 15486366]

87. Zhang Y, et al. Dietary and inhalation exposure to polycyclic aromatic hydrocarbons and urinary excretion of monohydroxy metabolites--a controlled case study in Beijing, China. Environ pollut Barking Essex. 1987;184:515–22.

88. Guo H, et al. Women are more susceptible than men to oxidative stress and chromosome damage caused by polycyclic aromatic hydrocarbons exposure. Environ Mol Mutagen. 2014;55(6):472–81. [PubMed: 24668722]

89. Wang Y, Zhu H, Kannan K. A review of biomonitoring of phthalate exposures. Toxics. 2019;7(2):21. [PubMed: 30959800]

90. Zota AR, Calafat AM, Woodruff TJ. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001-2010. Environ Health Perspect. 2014;122(3):235–41. [PubMed: 24425099]

91. Gascon M, et al. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol. 2015;135(2):370–378.e7. [PubMed: 25445825]

92. Jahreis S, et al. Maternal phthalate exposure promotes allergic airway inflammation over 2 generations through epigenetic modifications. J Allergy Clin Immunol. 2018;141(2):741–53. [PubMed: 28392331]

93. Ku HY, et al. Prenatal and postnatal exposure to phthalate esters and asthma: a 9-year follow-up study of a taiwanese birth cohort. PloS one. 2015;10(4):e0123309–9. [PubMed: 25875379]

94. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2017;56(3):308–21.

95. Fuseini H, Newcomb DC. Mechanisms Driving Gender Differences in Asthma. Curr Allergy Asthma Rep. 2017;17(3):19–9. [PubMed: 28332107]

96. Ketema RM, et al. Phthalates mixture on allergies and oxidative stress biomarkers among children: the Hokkaido study. Environ Int. 2022;160:107083. [PubMed: 35051840]

97. Predieri B, Alves CAD, Iughetti L. New insights on the effects of endocrine-disrupting chemicals on children. J Pediatr. 2022;98 Suppl 1(Suppl 1):S73–s85.

98. Zanobetti A, et al. Childhood asthma incidence, early and persistent wheeze, and neighborhood socioeconomic factors in the ECHO/CREW Consortium. JAMA Pediatr. 2022;176(8):759–67. [PubMed: 35604671]

99••. James-Todd T, Senie R, Terry MB. Racial/ethnic differences in hormonally-active hair product use: a plausible risk factor for health disparities. J Immigr Minor Health. 2012;14(3):506–11. [PubMed: 21626298] The paper summarizes racial differences in exposure to endocrine disrupting compounds.

100. Pollack CE, et al. Association of a housing mobility program with childhood asthma symptoms and exacerbations. Jama. 2023;329(19):1671–81. [PubMed: 37191703]

Table 1

Summary of studies of phenols, polyaromatic hydrocarbons, and phthalates and asthma-related outcomes in children

Chemical class	Chemical	Summary of evidence	Important modifiers
Phenols	Triclosan	Overall, studies support an association of triclosan with risk of asthma in children [26,35•]. Among children with asthma, the likelihood of reporting an asthma attack increased with increasing concentrations of TCS [36]. There is also evidence that prenatal exposure to TCS is associated with increased odds of probable asthma [37].	**Sex** Effects are stronger in male children [26]. Increasing concentrations of maternal plasma TCS were significantly associated with increased odds of asthma or wheeze in males, but decreased odds of asthma or wheeze in females [38]. However, one study reported that once stratifying by infant sex, the triclosan concentrations were associated with increased odds of probable asthma among girls [37]. **Eczema** No significant modification of the association between concentrations of TCS and aeroallergen sensitization, asthma, or wheeze. However, eczema did significantly modify the association between TCS concentrations and food sensitization [35].
	Parabens	Associations of parabens with asthma-related and allergic outcomes in children are inconsistent. Some studies report no association between methyl or propyl paraben with environmental sensitization, asthma, or recurrent wheeze [38] or between parabens and asthma attacks or ED visits among children with asthma [22]. Other studies report an inverse association with increasing concentrations of propyl paraben associated with decreased odds of probable asthma [37] and reduced rates of bronchiolitis and wheezing. Conversely, one study reported a positive association between ethyl-paraben and increased rates of asthma [40].	**Sex** The association between exposure to parabens on asthma and allergic outcomes is stronger in male children relative to female children. One study of asthmatic children found a positive association between male children's urinary concentrations of parabens and odds of environmental sensitization 38. Another study reported that among boys with asthma, increases in MP and PP concentrations were associated with an increased prevalence odds of reporting an ED visit in the past 12 months. This association persisted in a dose-response fashion [22].
	Bisphenols	Exposure to Bisphenol-A is associated with asthma and allergy outcomes in childhood. Exposure to BPA during the prenatal period is associated with increased odds of ever being diagnosed with asthma [21], positively associated with wheezing, asthma, eczema/rashes or hives, and aeroallergies [25] as well as increased risk of wheeze/asthma [72]. When considering exposure during childhood, increasing concentrations of BPA were associated with increased odds of general symptom days and emergency department visits [73]. Replacement bisphenols (BPF and BPS) may be an important contributor to asthma/allergy among children; however, findings have been inconsistent [73], though one study found that urinary concentrations of BPF were positively associated with current asthma and BPS concentrations were associated with increased odds of asthma without hay fever [70].	**Sex** The association between prenatal urinary BPA concentrations and asthma/allergy outcomes is modified by sex such that boys have increased odds of ever being diagnosed with asthma [21] and increased odds of symptom days and health care utilization [73], relative to girls in which associations were null.
	Others	2,5-DCP is associated with eczema and allergy outcomes among male children [21].	**Sex** Stratification by child sex revealed that these associations were being driven by consistent significant positive associations in boys but null associations for girls [21].
Polycyclic Aromatic Hydrocarbons (PAH)	Individual and Summary PAH metabolites	Overall, childhood exposure, though not prenatal [75, 82], to summarize PAH and some individual PAH metabolites was associated with an increased risk of wheeze [77], cockroach sensitization [79], and asthma-related emergency room visits [81].	**Tobacco smoke** Children exposed to tobacco smoke [75, 82] or with obesity [76] is more susceptible to asthma-related outcomes attributed to PAHs

Chemical class	Chemical	Summary of evidence	Important modifiers
Phthalates	Pyrene	Repeated gestational and childhood exposure to pyrene (including pyrene metabolite 1-hydroxypyrene [1-OHP]) was associated with asthma development and related symptoms in childhood [78, 80,].	**Atopy** Non-atopic (total indoor IgE level < 50 IU/mL) children may be more susceptible to pyrene [78], and associations may be mediated by 8OHdG as a marker of oxidative stress [80].
	Low molecular weight phthalates	Overall, null associations were observed between summary low molecular weight phthalates and asthma- and allergy-related outcomes in children [21], with one study observing that gestational mono-n-butyl phthalate, a metabolite of butyl benzyl phthalate (BBP), was associated with increased risk of asthma in children [89].	**Sex** There is some evidence to suggest that boys, but not girls, are susceptible to low molecular weight phthalates in relation to asthma and wheeze [21].
	High molecular weight phthalates	Several studies, but not all [21], observed associations between individual or summary high molecular weight phthalates and asthma-related outcomes in children, including metabolites diethyl phthalate (DEP) and butylbenzyl phthalate (BBzP), monocarboxyisooctyl phthalate (MCOP), mono (carboxynonyl) phthalate (MCNP), and summary di-2-ethyl-hexyl phthalate (DEHP) levels during gestation [15, 87, 88, 90] and childhood [11, 90].	**Wheeze** Children with wheeze may be more susceptible to the adverse effects of BBzP [11]. **Sex** While most studies observed that boys are more susceptible than girls [40, 90] was not consistently reported [88].
	Phthalate mixtures	Several studies investigated mixtures of phthalates in relation to asthma-related outcomes in children and found childhood mixtures to be associated with wheeze and eczema, of note – major contributors to the mixture were high molecular weight phthalates [93].	**Sex** Sex-specific effects were observed, suggesting effects of phthalate mixtures on asthma outcomes are specific to boys [31].