Environ Geochem Health
https://doi.org/10.1007/s10653-018-0201-1

ORIGINAL PAPER

Interactions between polycyclic aromatic hydrocarbons and epoxide hydrolase 1 play roles in asthma

Qihua Wang · Xijin Xu · Xiaowei Cong · Zhijun Zeng · Long Xu · Xia Huo

Received: 30 December 2017 / Accepted: 29 September 2018

Abstract Asthma, as one of the most common chronic diseases in children and adults, is a consequence of complex gene–environment interactions. Polycyclic aromatic hydrocarbons (PAHs), as a group of widespread environmental organic pollutants, are involved in the development, triggering and pathologic changes of asthma. Various previous studies reported the critical roles of PAHs in immune changes, oxidative stress and environment–gene interactions of asthma. *EPHX1* (the gene of epoxide hydrolase 1, an enzyme mediating human PAH metabolism) had a possible association with asthma by influencing PAH metabolism. This review summarized that (1) the roles of PAHs in asthma—work as risk factors; (2) the possible mechanisms involved in PAH-related asthma—through immunologic and oxidative stress changes; (3) the interactions between PAHs and *EPHX1* involved in asthma—enzymatic activity of epoxide hydrolase 1, which affected by *EPHX1* genotypes/SNPs/diplotypes, could influence human PAH metabolism and people's vulnerability to PAH exposure. This review provided a better understanding of the above interactions and underlying mechanisms for asthma which help to raise public's concern on PAH control and develop strategies for individual asthma primary prevention.

Keywords Polycyclic aromatic hydrocarbons (PAHs) · Asthma · Epoxide hydrolase 1 (*EPHX1*) · Airway inflammation · Oxidative stress

Q. Wang · X. Xu · X. Cong · Z. Zeng · L. Xu
Laboratory of Environmental Medicine and Developmental Toxicology, and Provincial Key Laboratory of Infectious Diseases and Molecular Immunopathology, Shantou University Medical College, Shantou, Guangdong, China

X. Xu
Department of Cell Biology and Genetics, Shantou University Medical College, Shantou, Guangdong, China

X. Huo (✉)
Laboratory of Environmental Medicine and Developmental Toxicology, Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, 601 Huangpu Avenue West, Guangzhou 510632, Guangdong, China
e-mail: xhuo@jnu.edu.cn

Introduction

Asthma is one of the most common chronic diseases (Global Initiative for Asthma 2018b). Approximately 334 million people suffer from asthma around the world with a prevalence ranging from 1 to 18% in different areas (Global Asthma Network 2014; Papi et al. 2018). In total, 14% of the children and 8.6% of young adults (18–45 years of age) around the world experience asthma symptoms, while 4.5% of young adults have been diagnosed with asthma and/or are taking treatment for asthma (Global Asthma Network

Published online: 06 October 2018

2014). The prevalence of asthma has increased during the past decades, particularly in westernized countries (World Allergy Organization 2013). Asthma is becoming increasingly common in developing countries because of increased industrialization and urbanization (World Allergy Organization 2013). From 2001 to 2010 in the USA alone, the overall prevalence of asthma has increased from 20.3 million (7.3%) to 25.7 million (8.4%), and asthma in children has increased from 8.7 to 9.3% (7.0 million) (Moorman et al. 2012). In Europe, asthma affects approximately 30 million children and adults under 45 years of age, with a prevalence ranging from 3 to 9% (European Respiratory Society 2013). The prevalence of asthma in China from 2000 to 2010, in urban settings has increased from 1.59 to 2.11% in children (0–14 years of age) and to 1.2% in adults (> 14 years of age) (Feng et al. 2014; Sha et al. 2015). As the 14th most important disorder in the world in terms of the extent and duration of disability, asthma places a heavy economic burden on families and countries globally (Global Asthma Network 2014).

Host-environment interactions in asthma have been studied over different spatial scales and timescales, such as CD14-endotoxin, HLA-allergens and ORMDL3-tobacco smoke, but they cannot fully explain the pathogenesis of asthma (Lee et al. 2015; Papi et al. 2018). Host factors include age, gender and genetic predisposition. Among them, SNPs and epigenetics have attracted a lot of attention in recent years (Lee et al. 2015). Polymorphisms for immune-related genes (*IL33*, *IL1RL1/IL18R1*, *HLA-DQ*, *SMAD3*, *IL2RB9*, *TSLP*) and airway function-related genes (*ZPBP2*, *GSDMB*, *ORMDL3*) have been studied in previous host-environment studies of asthma (Miller et al. 2018; Papi et al. 2018; Torgerson et al. 2011). Environment factors inducing to asthma include indoor and outdoor pollution, allergens, microorganism and cigarette smoke (Lee et al. 2015). Among them, varieties of air pollution (sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone, particulate matter with aerodynamic diameters less than 10 and 5 μm) have attracted a lot of attentions in recent years, whereas the effects of individual compounds are needed to be examined (Hehua et al. 2017; Zhang et al. 2016). For the most complex future scenario in which both genes and environment are unknown, large sets of environmental exposures and specific asthma phenotypes need to be defined (Lee et al. 2015).

Polycyclic aromatic hydrocarbon (PAH) is an environmental risk factor for asthma proved by amounts of epidemiologic studies, but the specific and quantitative relationships between PAH exposure and asthma, as well as underlying mechanisms, are unclear. Many studies focus on the involvement of complex PAH mixtures in asthma, such as vehicle exhaust, PM 2.5, tobacco smoke, instead of individual PAHs. The reason may lie in the physical and chemical properties of PAHs. Consisting of two or more fused aromatic (benzene) rings, PAHs are naturally deposited in coal, crude oil, peat and lignite (World Health Organization 2010; International Programme On Chemical Safety 1998). PAHs are released as mixtures to atmosphere and soil by incomplete combustion during daily living (traffic-related emission, tobacco smoking, cooking and heating) and industrial activities (coal-fired power plants, electronic waste recycling, asphalt, foundries and blast furnaces) (Chen et al. 2017; Guo et al. 2011; International Programme On Chemical Safety 1998; Xu et al. 2015). People in various areas suffer from PAH exposure and related health risks (Chen et al. 2017; Gosai et al. 2017; Keshavarzifard et al. 2017; Qu et al. 2015). With high lipophilic nature, PAHs are easily absorbed into human body through ingestion, inhalation and dermal contact, and then distribute rapidly and widely in the body (World Health Organization 2010). Humans have a high biotransformation potential for PAH, and the half-life of PAH dietary exposure in human body was only 2.5–6.1 h (Li et al. 2012). Although PAHs do not accumulate in human body, their reactive metabolites bound covalently to proteins and nucleic acids which cannot be repaired, resulting in genotoxicity and further adverse effects in almost all systems, including respiratory system (Guo et al. 2011, 2012; International Programme on Chemical Safety 1998; World Health Organization 2010; Xu et al. 2015). There are complex relationships between PAH exposure and asthma development, and multiple potential mechanisms might involve in this web of causation, including inflammatory responses and oxidative stress pathways (Karimi et al. 2015). In order to develop effective asthma prevention, research is needed to clarify the exact associations between individual PAH and asthma.

EPHX1, the gene of epoxide hydrolase 1, is an uncertain risk factor for asthma (Lee et al. 2011; Wang

and Karmaus 2017). *EPHX1*'s genotype and diplotype are associated with enzymatic activity of epoxide hydrolase 1, a phase I metabolic enzyme involved in the in vivo metabolism of PAHs and other organics (Henkler et al. 2012; Tung et al. 2011). Interaction between *EPHX1* SNPs and Phthalate metabolite involved in asthma has been explored in the previous study (Wang and Karmaus 2017). Both Phthalate and PAHs are organic pollutants needing epoxide hydrolase 1 for phase I metabolism in vivo. It provides a possibility that the interaction between *EPHX1* SNPs and PAHs may be involved in asthma. Very few literature focused on the roles of interactions between PAHs and *EPHX1* in asthma, let alone the inconsistent conclusions deduced from them.

Pathogenesis of asthma has not been fully defined, which limit the opportunities to develop targeted primary prevention, so a better understanding of the environment-gene interaction between PAHs and *EPHX1* involved in asthma will provide a reference for asthma primary prevention measures (Beasley et al. 2015). In order to explore above questions, the authors worked on the research articles and reviews on patterns of PAH exposure and asthma from different countries. These articles were collected in PubMed and official websites of World Health Organization (http://www.who.int/), International Programme On Chemical Safety (http://www.inchem.org/documents/ehc/ehc/ehc202.htm), Global Initiative for Asthma 2018 (http://ginasthma.org/), Global Asthma Network (http://www.globalasthmanetwork.org/), European Respiratory Society (https://www.erswhitebook.org/), and NCBI (http://www.ncbi.nlm.nih.gov) and the searching criteria are below: combined the terms "asthma" and the subheadings "pathogenesis" "immunology" "airway inflammation" "oxidative stress" "SNPs," as well as "polycyclic aromatic hydrocarbons" and "epoxide hydrolase 1"; articles from the 5 years prior to 2018 were mostly used with some exceptions. According to these literature, this review is summarized into three parts: (1) the roles of PAH exposure in asthma; (2) the possible mechanisms involved in PAH-related asthma; and (3) the interactions between PAHs and *EPHX1* involved in asthma.

The roles of PAH exposure in asthma

In this part, we reviewed the complex relationships between PAH exposure and asthma.

PAHs and diagnosed asthma

Jung et al. reported in an inner-city cohort that indoor air exposure to high concentrations (prenatal > 2.61 ng/m^3 or current > 1.01 ng/m^3) of pyrene (a kind of semi-volatile PAHs) was positively associated with asthma in 5- to 6-year-old children (Jung et al. 2012). Liu et al. found positive associations between urinary 1-pyrene and risk of diagnosed asthma in 6- to 19-year-old children, between urinary 2-phenanthrene and risk of diagnosed asthma in 13- to 19-year-old boys (Liu et al. 2016). Compared to reference area, children in benzo[a]pyrene exposed area Ostrava have higher asthma prevalence up to the age of 3.5 years (Sram et al. 2013). Serum naphthalene and pyrene are higher in asthmatic subjects than non-asthmatic subjects (Al-Daghri 2008). Possible mechanisms were summarized by Burton et al. that prenatal exposure to PAHs may be setting the stage for childhood asthma through DNA methylation in fetal lung or immune system (Burton 2009).

PAHs and asthma clinical manifestations

Increased wheezing was found in asthmatic children exposed to air phenanthrene and 4- to 6-ring particle-bound PAHs (Gale et al. 2012). Positive association between 4-phenanthrene and risk of wheezing was found in 13- to 19-year-old girls (Liu et al. 2016). Prenatal exposure to PAHs from fossil fuel combustion is a risk factor for wheezing without cold and the duration of wheezing in the chest during the first year of life (Jedrychowski et al. 2005).

Exposure to PAHs has been reported to cause impaired lung function in asthmatics. Forced expiratory volume in 1s (FEV1) and forced vital capacity (FVC) of asthmatic children are negatively associated with benzo(a)pyrene, low molecular weight PAHs, high molecular weight PAHs and total PAHs (Smargiassi et al. 2014). Similar negative associations are found between 2- to 4-ring PAHs and FEV1, FVC in healthy Chinese (Zhou et al. 2016).

PAH exposure linked to asthma biomarkers, especially in allergic asthma. Specific immunoglobulin (Ig)E levels and eosinophil counts are the most consistent biomarkers for the identification of infants and preschool children at high risk of allergic asthma (Wandalsen et al. 2016). Naphthalene, 4H-cyclobenta[def]phenanthrene, pyrene and 1,2-benzanthracene were correlated with IgE in Arab children (Al-Daghri et al. 2013). Mice exposed to diesel exhaust particles contained 522 micrograms of PAHs that have significant increases in eosinophils (Stevens et al. 2009). In view of complex asthma phenotypes, the associations between PAHs and asthma biomarkers are extremely complex and need more studies to explore.

PAHs and asthma pathologic changes

PAH exposure contributes to airway hyperresponsiveness. Exposure to PAH mixture in common traffic-related air pollutants is associated with reduced β2-adrenergic receptor gene expression and increased airway hyperreactivity in mice, suggesting that PAH exposure may induce airway hyperreactivity via suppressing β2-adrenergic receptor (Chu et al. 2013). In addition, there is a possible immune mechanism involved in PAH-related airway hyperreactivity as well. PAH exposure has a positive association with total plasma IgE in both non-asthmatics and asthmatics (Hew et al. 2015). The higher the concentration of IgE, the easier it is for the bronchus to be provoked by methacholine (Sunyer and Munoz 1996). Increased IgE levels contribute to eosinophilic airway inflammation, which is associated with bronchial hyperresponsiveness both in symptomatic and asymptomatic persons (Jansen et al. 1999; Postma et al. 2015). It is confirmed in mice model studies on exposure to diesel exhaust particle PAHs or PAHs (Ren et al. 2014). In addition, PAHs contribute to significant increased eosinophils and further airway hyperresponsiveness via increasing Th2-mediated cytokines IL-5 and IL-13 (Ren et al. 2014; Stevens et al. 2009). IL-5 and IL-13 show strong correlations with airway hyperresponsiveness in adult asthma patients as well (Agache et al. 2016). It is deduced from above that PAH exposure can induce the releases of IL-5, IL-13 and IgE, which contribute to airway eosinophilia and further airway hyperresponsiveness.

PAHs contribute to the impaired reversion of airway obstruction in the asthmatic. After exposure to PAH mixture, the expression and function (receptor responsiveness) of β2-adrenergic receptor of murine tracheal epithelial cells and human airway smooth muscle cells were reduced, indicating that PAHs can impede β2-adrenergic receptor-mediated airway relaxation, possibly via agonist-induced receptor desensitization (Factor et al. 2011).

PAHs play roles in airway inflammation through T lymphocytes, eosinophils, basophils, mast cells, dendritic cells, neutrophils and macrophages (Eng and DeFelice 2016; Global Initiative for Asthma 2018a; Xu et al. 2017) (Fig. 1). ① Type-2 inflammation: PAH-mediated Th2 skewing stimulates B cells to produce allergen-specific IgE and further induces eosinophilic airway inflammation (Karimi et al. 2015; Postma et al. 2015). Similarly, serum PAH levels are positively associated with IgE, in line with the fact that asthmatic children have higher PAH and IgE levels than non-asthmatic children (Al-Daghri et al. 2013; Wandalsen et al. 2016). Asian sand dust-bound PAHs contribute to the aggravation of ovalbumin-induced lung eosinophilia in mice (Ren et al. 2014; Wandalsen et al. 2016). PAHs in vehicle-emitted particles are proved by studies on allergic human and mice to induce basophil activation and increase basophil percentages (Lubitz et al. 2010; Zakharenko et al. 2017). ② Other inflammations: PAHs influence regulatory T cell (Treg)/Th17/Th22 balance through aryl hydrocarbon receptor (AhR), a transcription factor involved in Th17-/Th22-type polarization, and further neutrophil recruitment in both healthy and asthmatic people (Ple et al. 2015). Similarly, exposure to 100 mg/kg vehicle exhaust-PAHs increases neutrophil percentage in mice (Zakharenko et al. 2017). Degranulation and cytokine release from above-activated immune cells contribute to airway smooth muscle contraction and proliferation, while lung epithelium-derived cytokines also activate above innate immune cells, creating a feedback loop perpetuating asthma (Galowitz and Chang 2015).

PAHs are involved in airway remodeling through eosinophils, mast cells and vascular endothelial growth factor (VEGF) (Bakakos et al. 2016; Grainge et al. 2016; Kudo et al. 2013). PAH-mediated Th2 skewing can lead to chronic eosinophilic inflammation, contributing to airway remodeling and the development of fixed airflow obstruction in the long

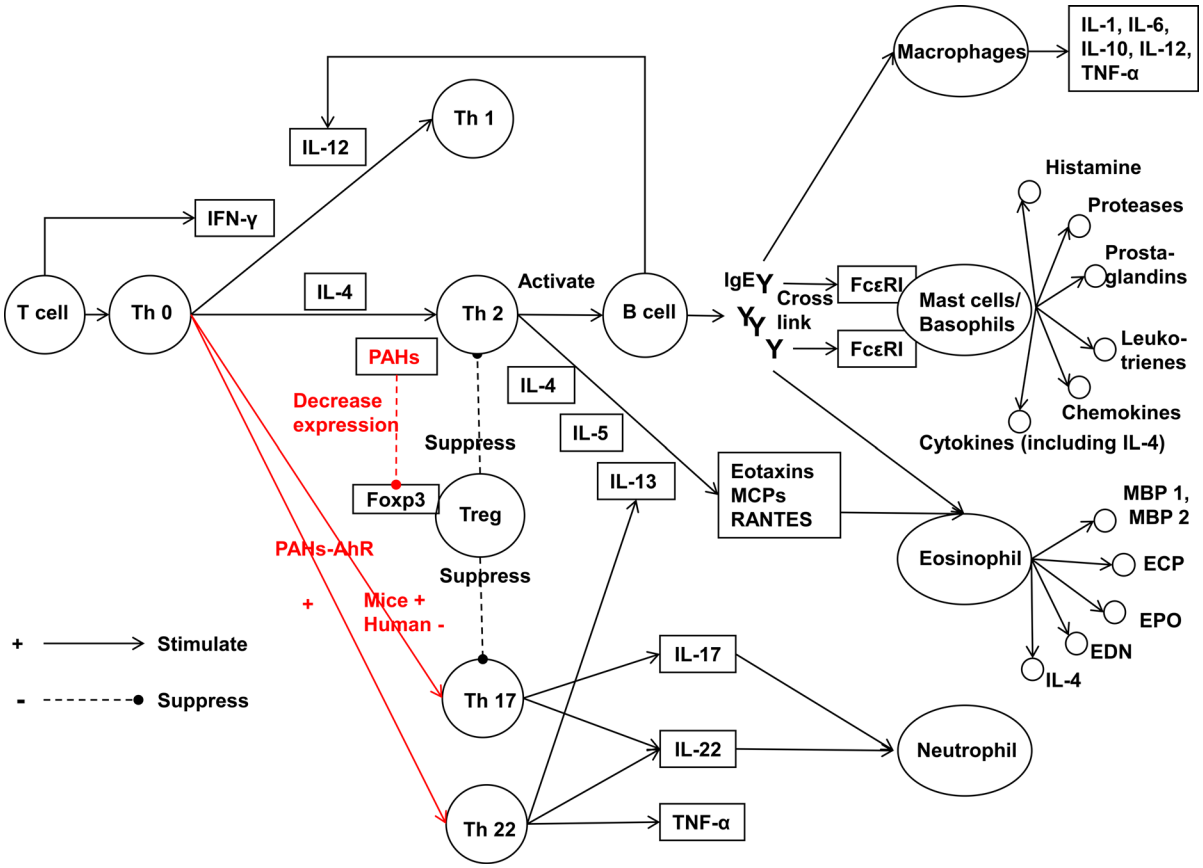

Fig. 1 Effects of PAHs on immune changes involved in asthma. Th2 and Th17 suppressions by Treg are decreased by PAHs. Th17 is downregulated, while Th22 is upregulated by PAHs bonding to AhR. (Eng and DeFelice 2016; Global Initiative for Asthma 2018a; Xu et al. 2017; Harper and Zeki 2015; Kudo et al. 2013; Toldi et al. 2011). MBP major basic proteins; ECP eosinophil cationic protein; EPO eosinophil peroxidase; EDN eosinophil-derived neurotoxin; MCP monocyte chemoattractant protein; RANTES (CCL5) Chemokine (C–C motif) ligand 5

term (Postma et al. 2015). Diesel exhaust particle PAH and benzo(a)pyrene exposure exacerbate IL-22 secretion but inhibit the production of IL-17A through AhR (Ple et al. 2015). IL22 plays roles in neutrophil recruitment, airway smooth muscle proliferation and tissue remodeling (Ple et al. 2015). Exposure to PAHs (AhR ligands) stimulates the degranulation of mast cell, releasing histamine, heparin and tryptase (Modena et al. 2016; Zhou et al. 2013). Increased tryptase can stimulate fibroblast mitogen and type-1 collagen synthesis, leading to airway smooth muscle proliferation (Modena et al. 2016; Zhou et al. 2013). In addition, PAHs induce VEGF through PI-3 K/AP-1-dependent and HIF-1a-independent pathways (Ding et al. 2006). VEGF plays a major role in enhanced vascular permeability and plasma exudation, which enables inflammatory cells and other plasma components to reach extravascular inflammatory sites, a key process of inflammation (Bakakos et al. 2016). Furthermore, VEGF is also involved in enhanced allergic sensitization, and upregulates subsequent Th2-type inflammatory responses, monocyte chemotaxis, eosinophil chemotaxis and airway edema (Bakakos et al. 2016; Kim et al. 2010).

To explore the exact roles of PAH exposure in asthma risk, we listed the data of previous studies in Table 1. We summarized that prenatal and postnatal PAH exposure both can lead to asthma risk. Pyrene, phenanthrene and total airborne PAHs were risk factors for diagnosed asthma, and it seems that total airborne PAHs had bigger effect than individual PAHs. Total airborne PAH was a risk factor for

Table 1 PAHs and asthma

	Author	Population	Exposure duration	Detected substance	Pollutants	Outcomes	RR (95%CI) or OR (95%CI)
Diagnosed asthma	Jung et al. (2012)	Children at 5–6 years of age	Prenatal exposure (personal air monitoring during 48 h) Exposure at 5–6 years of age (2-week residential monitoring)	Residential air	High pyrene during pregnancy (> 2.61 ng/m^3) and 5–6 years of age (> 1.01 ng/m^3)	Diagnosed asthma	OR = 1.90 (1.13, 3.20) in whole children OR = 2.89 (1.77–5.69) in non-atopic children
	Jung et al. (2014)	Children at 5–6 years of age	Monitor 2 weeks	Residential air	3- to 6-ring PAHs	Diagnosed asthma at age 5 years	1-methylphenanthrene: RR = 2.62 (1.17–5.88) 9-methylphenanthrene: RR = 2.17 (1.06–4.45) 3,6-dimethylphenanthrene: RR = 2.69 (1.21–5.94) All in children with obesity
	Liu et al. (2016)	Participants aged 6–19 years	One spot individual exposure	Urine PAH metabolites	2- to 4-ring PAHs	Diagnosed asthma	1-pyrene quartile 4: OR = 1.444 (1.003–2.080) 2-phenanthrene in boys 13–19 years of age: OR = 2.35 (1.16–4.79)
	Wang et al. (2017)	Children at 6 years of age	Individual exposure 3 years ago	Urine PAH metabolite	1-hydroxypyrene	Diagnosed asthma	OR = 1.42 (1.18–1.70)
	Jedrychowski et al. (2014)	4 year-follow-up from pregnancy	Prenatal and postnatal exposure	Personal indoor airborne PAH monitor	Total airborne PAHs	Diagnosed asthma	OR = 7.80 (1.40, 43.47)

Table 1 continued

	Author	Population	Exposure duration	Detected substance	Pollutants	Outcomes	RR (95%CI) or OR (95%CI)
Asthma symptoms	Liu et al. (2016)	Participants aged 6–19 years	One spot individual exposure	Urine PAH metabolites	2- to 4-ring PAHs	Ever wheeze	4-phenanthrene in girls 13–19 years of age: OR = 4.086 (1.326–12.584)
	Gale et al. (2012)	Children 6–11 years of age	Measured at 1-min intervals and aggregated into 24-h daily averages	Ambient particle-bound PAH	PAHs with 3 rings or more	Self-reported wheeze	1 day: OR = 1.04 (1.01, 1.07) 14 days ago: OR = 1.06 (1.01, 1.13) 14-day moving average: OR = 1.01 (1.01, 1.02)
	Jedrychowski et al. (2014)	4 year-follow-up from pregnancy	Prenatal and postnatal exposure to PAHs	Personal indoor airborne PAH monitor	Total airborne PAHs	Recurrent wheezing	OR = 1.61 (1.16, 2.24)
Diagnostic biomarkers	Miller et al. (2010)	Children $\geq$ 5 year old	Current individual exposure	Urine PAH metabolites	2- to 4-ring PAHs	Allergen (mouse)-specific IgE	2-hydroxyfluorene: OR = 1.82 (1.01, 3.28) 3-hydroxyfluorene: OR = 2.21 (1.18, 4.19) 1-hydroxyphenanthrene: OR = 1.88 (1.03, 3.49) 3-hydroxyphenanthrene: OR = 2.08 (1.09, 4.00)
	Wang et al. (2017)	Children at 6 years of age	individual exposure 3 years ago	Urine PAH metabolite	1-hydroxypyrene	serum IgE	$\beta = 0.27$, $p = 0.027$

Table 1 continued

	Author	Population	Exposure duration	Detected substance	Pollutants	Outcomes	RR (95%CI) or OR (95%CI)
Lung function	Zhou et al. (2016)	Residents aged 18–80 years	Individual exposure	Urinary PAH metabolites	2- to 5-ring PAHs	FEV1	Estimated Changes in ml (95% CI)
							2-OHNap: − 23.79 (− 42.00, − 5.59)
							9-OHFlu: − 19.36 (− 33.64, − 5.09)
							2-OHFlu: − 41.76 (− 63.24, − 20.28)
							1-OHPhe: − 39.53 (− 60.74, − 18.33)
							2-OHPhe: − 34.35 (− 52.58, − 16.12)
							3-OHPhe: − 27.37 (− 46.30, − 8.44)
							4-OHPhe: − 36.87 (− 56.12, − 17.62)
							9-OHPhe: − 33.47 (− 52.98, − 13.96)
							1-OHPyr: 25.03 (− 41.99, − 8.07)
							∑OH-PAHs: − 37.13 (− 58.59, − 15.68)
						FVC	2-OHNap: − 24.39 (− 46.66, − 2.12)
							2-OHFlu: − 33.90 (− 59.89, − 7.90)
							1-OHPhe: − 28.56 (− 54.23, − 2.90)
							2-OHPhe: − 27.46 (− 49.76, − 5.16)
							4-OHPhe: − 27.15 (− 50.51, − 3.80)
							∑OH-PAHs: − 27.99 (− 54.26, − 1.71)

Table 1 continued

	Author	Population	Exposure duration	Detected substance	Pollutants	Outcomes	RR (95%CI) or OR (95%CI)
	Smargiassi et al. (2014)	Children 7–12 years of age	Personal pesticide sampling. 10 consecutive days	Ambient PAHs	Benzene, Benzo(a)Pyrene, low molecular weight PAHs, high molecular weight PAHs	FEV1, FVC, FEF25–75%	No significant association
Immune Changes	Lubitz et al. (2010)	23–35 years of age	Human basophils	Diesel exhaust particles- PAH	B[a]P and Phe	IL-4 and IL-8 secretion from enriched basophils	Increase in birch pollen-allergic individuals who were exposed to B[a]P or Phe
	Al-Daghri et al. (2014)	Rats	Treated with benzopyrene	–	Benzopyrene	IL-4 mRNA in whole blood	$\beta = 0.36$, $p < 0.001$
	Al-Daghri et al. (2013)	$\leq$ 15 years of age	Individual exposure	Serum PAHs	Various PAHs	IL-4 IL-5 IgE	Positive correlation
	Al-Daghri et al. (2013)	$\leq$ 15 years of age	Individual exposure	Serum PAHs	Various PAHs	IL-8 IL-10 IFN-γ	Negative correlation
	Ple et al. (2015)	Human peripheral blood mononuclear cells (PBMCs)	PBMCs were treated by PAH standard reference material and different purified PAHs	Diesel exhaust particle (DEP)-PAH and Benzo[a]Pyrene (B[a]P)	IL-22 IL-17A	Increased IL-22 but decreased IL-17A production in both healthy and asthmatic subjects	

wheeze. Fluorene that has a bigger effect on lung function than other 2- to 5-ring PAHs. In view of that people in different areas and ages have different susceptibilities to PAH exposure, further meta-analyses are need to explore the exact effects of individual PAHs. Furthermore, genetic susceptibilities should be taken into account.

Possible mechanisms involved in PAH-related asthma

According to previous studies, we summarized that several kinds of PAHs may increase the onset, symptoms, biomarkers and pathological changes of asthma. Although the responsible mechanisms in PAH-related asthma are not well understood, it was deduced that inappropriate changes in immune system and oxidative stress as well as PAH-*EPHX1* interaction may play roles (Ghosh et al. 2016; Tung et al. 2011; Wandalsen et al. 2016).

Immunologic mechanisms

Asthmatic patients have an imbalance of Treg/Th1/Th2/Th17/Th22 cells: decreased Th1/Th2 ratio, increased Th17/Treg ratio and increased Th22. PAHs are involved in above imbalance and further changes in immune molecules (immunoglobulins, cytokines, inflammatory mediators) and inflammatory cells (T cells, B cell, eosinophil, basophil, mastocyte, neutrophils, macrophages) (Harper and Zeki 2015; Kudo et al. 2013; Toldi et al. 2011) (Fig. 1).

Treg/Th1/Th2/Treg/Th17/Th22 imbalance

PAHs induce DNA methylation of CpG sites within the Forkhead Box P3 (FoxP3) promoter and thus reduce FoxP3 expression in Treg cells, resulting in Treg dysfunction: decreased Th2 suppression and increased Th2-mediated inflammation (Hew et al. 2015). PAHs play roles in Th17/Th22-type polarization through AhR, a transcription factor involved in the development of the Th17 and Th22 subsets (Ple et al. 2015). In mice, PAHs in standardized particulate matter sample, diesel exhaust and cigarette-smoke extract enhance Th17 differentiation (van Voorhis et al. 2013). In human, Th17 is downregulated, while Th22 is upregulated by PAH exposure (Ple et al. 2015).

Further variation of T helper cell-mediated cytokine

PAHs have been shown in previous studies to be associated with decreased Th1-mediated cytokine (IFN-γ) and increased Th2-mediated cytokines (IL-4, IL-5 and IL-13), which resulted from Th2 skewing, favoring an increase in sensitization of type-1 hypersensitivity involved in asthma (Al-Daghri et al. 2013; Hew et al. 2015). After PAH exposure, IL-17 (Th17-mediated cytokine) levels are increased in mice but decreased in human both through AhR, indicating possible species-specific effects of AhR agonists (Hong et al. 2016; Ple et al. 2015). PAHs (AhR agonists) increase IL-22 production but not IL-17 production in human through Th22 but not Th17 (Trifari et al. 2009). Furthermore, PAHs are negatively associated with IL-10, and low levels of IL10 play a role in the pathogenesis of asthma (Al-Daghri et al. 2013; Bohm et al. 2015; Hew et al. 2015). Epigenetics is one of the mechanisms of PAH-related cytokine changes. Maternal exposure to benzo[a]pyrene was associated with hypermethylation of IFN-γ but not IL-4 in cord blood DNA from cohort children (Tang et al. 2012). Increased IL-4 mRNA expression and polyaromatic hydrocarbon concentrations were found in children with asthma (Al-Daghri et al. 2014). The expression of IL-4 mRNA in whole blood from rats treated with benzopyrene was higher than healthy control (Al-Daghri et al. 2014).

Further immunocyte activation and airway inflammation

PAHs enhance allergic inflammation and stimulate inflammatory responses through increasing IgE production mediated by productions of cytokines and chemokines, as well as the activation of macrophages and other mucosal cell types (Nel et al. 1998). Macrophage-derived cytokines induced by PAH exposure, namely IL-1, IL-6, IL-10, IL-12 and TNF-α, are important in allergic inflammation (Nel et al. 1998). When allergens cross-link with sensitized basophils and mast cells directly or through IgE, basophils and mast cells are activated and subsequently release anaphylactogenic mediators, such as histamine, proteases, prostaglandins, leukotrienes, chemokines and cytokines, responsible for the classical symptoms of the immediate phase (type-1 hypersensitivity) (Akdis and Akdis 2015; Chinthrajah et al.

2016). These basophil- and mast cell-released substances and their roles in airway pathological changes are showed in Table 2 (Modena et al. 2016). On the other hand, PAHs increase eosinophil quantity in mouse bronchoalveolar lavage fluid (Stevens et al. 2009). Eosinophils contribute to allergic airway inflammation, later development and severity of asthma in infants and preschool children by releasing granule components, secreting cytokines and regulating T cells (Ren et al. 2014; Wandalsen et al. 2016; Wilkerson et al. 2016). Pro-inflammatory and Th2 cytokine production induced by PAH exposure can stimulate the expression of eotaxin mRNA, a chemotactic factor that regulates eosinophils, and further induce eosinophils to secrete intracellular crystalloid granules (cell degranulation) (Ravin and Loy 2016). Cationic granular proteins released by activated eosinophil and their roles in airway pathological changes are showed in Table 2 (Chatzileontiadou et al. 2015; Morgan et al. 2005; Xia et al. 2016). This degranulation, in target airway tissues and respiratory secretions, is considered a key pathogenic mechanism in asthma because it induces tissue damage and dysfunction (Martinez-Giron and Martinez-Torre 2016).

Oxidative stress mechanisms

8-OHdG was used as a sensitive biological marker of oxidative DNA damage (Zhou et al. 2016). Increased reactive oxygen species (ROS) and reactive nitrogen species are found in asthmatic patients, and they induce asthmatic airway inflammation via pro-inflammation pathways (Andreadis et al. 2003; Guo et al. 2000; Zuo et al. 2013). H_2O_2 and O_2^- are produced during PAH metabolisms in human body (Fig. 2), and the ROS produced by PAHs probably contribute to asthma through immune response and direct airway damage as follows: ROS produced by PAH metabolism lead to transcriptional upregulation of genes involved in immune regulation and activate the promoters of cytokines and chemokines involved in allergic inflammation through activator protein-1 and NF-κB signaling pathways, which may explain the exacerbation of allergic inflammation (Henkler et al. 2012; Karimi et al. 2015; Nel et al. 2001). Furthermore, oxidants produced by PAH metabolism can impair cilia function, reduce surfactant activity, injure fibroblasts, promote epithelial permeability, and make other effects which could diminish lung mechanics and/or lung repair mechanisms (Repine et al. 1997). PAHs in diesel exhaust particles also induce apoptosis and necrosis in bronchial epithelial cells via a mitochondrial pathway (Nel et al. 2001).

PAH-*EPHX1* interactions

EPHX1 expresses epoxide hydrolase 1, a protein-coding gene located at position 1q42.1. It is a critical biotransformation enzyme in the activation and detoxification of epoxides and in the metabolism of reactive oxidants. This gene has been shown to be involved in several human diseases including asthma (Ghosh et al. 2016; NCBI 2017; Salam et al. 2007; Vaclavikova et al. 2015).

EPHX1 polymorphisms, genotypes, diplotypes and enzymatic activities (Table 3) are associated with risks of lifetime, current, early-onset, early-persistent and late-onset asthma (Salam et al. 2007; Tung et al. 2011). Tung KY et al. found that Tyr/His and His/His at codon 113, Arg/Arg and Arg/His at codon 139, as well as 113His-139Arg and 113Tyr-139Arg diplotypes, were risk factors for lifetime asthma and early-onset asthma (risk: Tyr/His > His/His at codon 113, Arg/Arg > Arg/His at codon 139, 113His-139Arg > 113Tyr-139Arg) (Tung et al. 2011). Similarly, His/Arg at codon 139, 113His-139Arg, 113Tyr-139Arg, 113Tyr-139His and high *EPHX1* metabolic phenotype were risk factors for lifetime asthma, current asthma, early persistent asthma and late-onset asthma (Salam et al. 2007). Meanwhile, polymorphic *EPHX1* alleles in exon 3 and exon 4, as well as *EPHX1* diplotypes, are associated with altered *EPHX1* activity (Ghosh et al. 2013) (Table 3). These results suggest that *EPHX1* SNPs, genotypes and diplotypes related to higher EPHX1 activities are associated with higher asthma risk. The underlying mechanism is probably related to PAHs: high-activity *EPHX1* produces excessive catechols as well as further hydrogen peroxide and superoxide anion during PAH metabolism in vivo (Fig. 2), leading to increased oxidative stress and ROS-mediated airway damage (Tung et al. 2011). In addition, *EPHX1* genotypes play roles in genetic susceptibility to DNA damage, chromosomal aberrations and epigenetic changes due to environmental exposure, which can explain the difference of asthma risk in people with different *EPHX1* SNPs, genotypes,

Table 2 Roles of mast cells (basophils) and eosinophils in asthma

Activated cells	Stimulating factor		Activation mechanisms	Contents of cell degranulation	Functions of the cell degranulations
Mast cells (or) basophils (Modena et al. 2016)	IgE (or) allergen	Cross-link with high-affinity IgE receptor (FcεRI) on basophils and mast cells	Activate inositol trisphosphate 3, leading to elevation of intracellular calcium and further degranulation	Histamine	Induce airway smooth muscle proliferation
				Heparin	Cause immediate bronchoconstriction via histamine H1 receptors
					Correlates with bronchial hyperreactivity
				Proteases (tryptase)	As mitogens for fibroblasts, stimulate the synthesis of type-1 collagen, play roles in airway smooth muscle proliferation and histamine–induced contraction
					Degrade vasoactive intestinal peptide (vasodilator)
					Associated with airway remodeling
			Convert arachidonic acid to eicosanoids	Prostaglandins	Cause smooth muscle contraction
				Leukotrienes (Leukotriene C_4, D_4, E_4)	Increase vascular permeability
					Stimulate mucus secretion
					Recruit effector cells
			Influence gene transcription of cytokines by activating protein kinase B, protein kinase C, c-Jun N-terminal kinase, p38 and extracellular regulated protein kinases	IL-4 and IL-13	Contributes to the development of Th2 cells and stimulates Th2 cell responses
				IL-3, IL-5 and GM-CSF	Promote eosinophil production and activation
				Tumor necrosis factor-α (TNF-α)	Promotes inflammation: stimulates cytokine production by many cell types
					activates endothelium

Table 2 continued

Activated cells	Stimulating factor		Activation mechanisms	Contents of cell degranulation	Functions of the cell degranulations
Eosinophils	IL-4 (Verma et al. 2017)	IL-4 receptor	Exocytosis, piecemeal degranulation and cytolysis (granule release)	IL-4	Contributes to the development of Th2 cells and stimulates Th2 cell responses
				Major basic proteins (Morgan et al. 2005)	Induces nuclear factor-kappa B (NF-κB) activation via extracellular regulated protein kinase 1 or 2 and protein kinase B, activating transcription of pro-inflammatory cytokines
	IL-5 family cytokines (IL-5, IL-13, GM-CSF) (Ravin and Loy 2016)	IL-5 family cytokine receptors IL-5 regulates eosinophils differentiation and maturation by the mTOR pathway		Eosinophil cationic protein	Increases TNF-α production and triggers apoptosis by caspase-8 activation
	Eotaxins, monocyte chemoattractant proteins and chemokine (C–C motif) ligand 5	G protein-coupled receptors		Eosinophil peroxidase	Oxidize substrates based on peroxide. Involved in oxidative stress
				Eosinophil-derived neurotoxin (Chatzileontiadou et al. 2015)	Displays limited cytotoxicity against respiratory epithelial cells
					Enhances Th2 immune responses as a chemoattractant for human dendritic cells

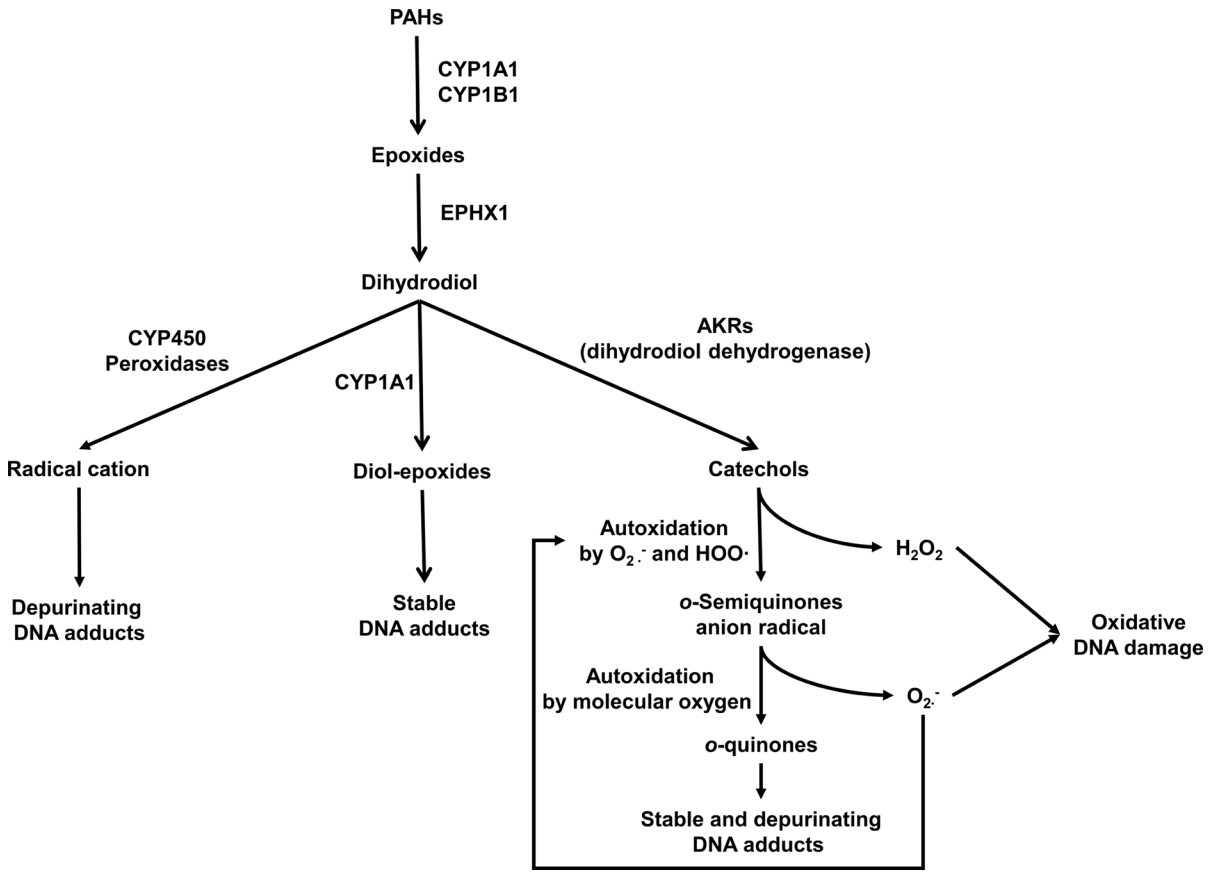

Fig. 2 Phase I metabolism of PAHs (Bolton et al. 2000; Henkler et al. 2012; McCoull et al. 1999). CYP1A1 cytochrome P4501A1; CYP1B1 cytochrome P4501B1; EPHX1 epoxide hydrolase 1; O_2^{-} superoxide anion; AKR: aldo–keto reductase

diplotypes from another perspective (Iarmarcovai et al. 2008; Stiborova et al. 2014; Vaclavikova et al. 2015; Xiang et al. 2012). DNA damage levels, as detected by DNA adducts, are higher in smokers with *EPHX1* Arg/Arg than Arg/His and His/His genotypes at codon 139, suggesting that a human with higher *EPHX1* activity is more impressionable to environmental exposure (Peluso et al. 2013). Consistent with this, increased micronuclei frequency (chromosomal aberrations) related to PAH exposure is associated with *EPHX1* exon 3 Tyr/Tyr and *EPHX1* exon 3 His/Tyr in coke-oven workers (*EPHX1* activity: Tyr/Tyr > His/Tyr > His/His at exon 3) (Iarmarcovai et al. 2008). Butadiene-exposed workers with intermediate/high-activity EPHX1 diplotypes have higher nucleoplasmic bridge frequency (chromosomal aberrations) than low-activity *EPHX1* diplotypes (Xiang et al. 2012). These studies proved that *EPHX1* genotypes and diplotypes related to higher EPHX1 activity are associated with DNA and chromosome damages due to PAH exposure, which contribute to genetic predisposition to asthma.

PAH exposure and *EPHX1* are both independent risk factors for asthma, the interactions between which are involved in asthma as well. *EPHX1* SNPs/genotypes/diplotypes and corresponding enzymatic activities influence PAH metabolism in vivo, as well as human vulnerability to PAH exposure (Ghosh et al. 2013; Tung et al. 2011). During metabolism in vivo, PAHs are oxidized to epoxide catalyzed by *CYP1A1* and *CYP1B1*, and then convert to dihydrodiol (diol) catalyzed by *EPHX1* (Henkler et al. 2012). The dihydrodiols further convert to diol-epoxides and produce DNA adducts or convert to catechols and further o-quinones, releasing hydrogen peroxide and superoxide anion (Bolton et al. 2000) (Fig. 2). As a result, EPHX1 activity, which is influenced by *EPHX1* SNPs/genotypes/diplotypes, is supposed to be

Table 3 Genotypes, SNPs, diplotypes and activities of *EPHX1*

	Genotype (Ghosh et al. 2013)			SNPs		
	Wild	Variant		SNP name (Ghosh et al. 2013)	Allele frequencies (1000 genomes) (NCBI 2018a, b)	Enzyme activity (Hassett et al. 1994)
EPHX1 in exon 3						
Genotype	TT; Tyr113Tyr	TC; Tyr113His	CC; His113His	rs1051740 (Tyr > His at codon 113 exon 3)	Minor Allele Count	
					Han Chinese in Beijing, China	$C = 0.3133$
					British in England and Scotland	$C = 0.4320$
					Esan in Nigeria	$C = 0.3571$
						$C = 0.1162$
Prevalence	46.5%	37.8%	15.6%			
						Replacing Tyr by His in position 113 results in a 39% decrease in epoxide hydrolase 1 activity
EPHX1 in exon 4						
Genotype	AA. His139His	AG; His139Arg	GG; Arg139Arg	rs2234922 (His > Arg at codon 139 exon 4)	Minor Allele Count	
					Han Chinese in Beijing, China	$G = 0.2155$
					British in England and Scotland	$G = 0.0971$
					Esan in Nigeria	$G = 0.1593$
						$G = 0.3485$
Prevalence	68.1%	27.7%	4.2%			
						Replacing His by Arg in position 139 results in a 25% increase in epoxide hydrolase 1 activity
EPHX1 diplotype (Ghosh et al. 2013)	113Tyr/Tyr-139His/Arg	113Tyr/Tyr-139Arg/Arg		113Tyr/His-139Arg/Arg		High
	113Tyr/Tyr-139His/His	113Tyr/His-139His/Arg		113His/His-139Arg/Arg		Intermediate
	113Tyr/His-139His/His	113His/His-139His/His		113His/His-139His/Arg		Low

positively associated with PAH-DNA adduct production and ROS production during PAH metabolism in vivo, contributing to PAH-related asthmatic airway damages. Correspondingly, DNA adducts produced during PAH metabolism can lead to point mutations such as G → T or A → T transversions, contributing to bigger possibility of general SNPs (Henkler et al. 2012). Although it is unclear whether PAH-related DNA adducts could cause specific SNPs in EPHX1, a possibility can be deduced. Above interaction between PAH and *EPHX1* provides a new idea of further research—a positive feedback loop of EPHX1-mediated asthma risk due to PAH exposure.

Conclusion

Despite various preventative activities aimed at reducing emissions over the decades, PAHs still are significant risk factors for asthma as well as other respiratory problems. The principal mechanisms by which PAHs contribute to asthma pathogenesis involve a complex interplay between genes, immune system and oxidative stress. Exact effects of each PAH on asthma risk need to be further explored. It is concluded from above that the risk of asthma due to PAH exposure is influenced by different activities of epoxide hydrolase 1, which are affected by *EPHX1* SNPs/genotypes/diplotypes. The reason is that activity of epoxide hydrolase 1 could alter human PAH metabolism and human vulnerability to PAHs. Mechanisms of the interaction between PAHs and *EPHX1* involved in asthma pathogenesis include ROS, immunological changes (including imbalance of Th1/Th2/Treg/Th17 and airway inflammation) and DNA damage.

Although PAHs have been reported as toxic chemicals and managed by Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) and other acts,they are still produced during daily life through vehicle exhaust emission, tobacco smoking, heating and cooking. PAHs play roles in various health risks, among which asthma is one of the top 5 respiratory diseases in the world, accounting for high mortality, morbidity and health-care costs worldwide (Chang 2013; Global Asthma Network 2014). As a result, more regulations and government policies should be made to control PAH pollution. On the other hand, this review probably provides new ideas of

asthma individual primary prevention: People with *EPHX1* SNPs/genotypes/diplotypes related to higher EPHX1 activity should take more attention to PAH exposure and asthma risk. In the future, more GWAS, meta-analysis of gene-environment interaction studies can increase driving power further and provide robust estimates of gene-environment interactions.

Acknowledgements This study was supported by the National Natural Science Foundation of China (21876065) and the Department of Education of Guangdong Government under the Top-tier University Development Scheme for Research and Control of Infectious Diseases (2016046). We would like to thank Dr. Stanley Lin for his constructive comments and English language editing.

Funding This study was funded by National Natural Science Foundation of China (Grant Number 21876065) and the Department of Education of Guangdong Government Top-tier University Development Scheme for Research and Control of Infectious Diseases (Grant Number 2016046).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

References

Agache, I., Strasser, D. S., Klenk, A., Agache, C., Farine, H., Ciobanu, C., et al. (2016). Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. *Allergy, 71*(8), 1192–1202.

Akdis, C. A., & Akdis, M. (2015). Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. *World Allergy Organization Journal, 8*(1), 17. https://doi.org/10.1186/s40413-015-0063-2.

Al-Daghri, N. M. (2008). Serum polycyclic aromatic hydrocarbons among children with and without asthma: Correlation to environmental and dietary factors. *International Journal of Occupational Medicine and Environmental Health, 21*(3), 211–217.

Al-Daghri, N. M., Abd-Alrahman, S., Draz, H., Alkharfy, K., Mohammed, A. K., Clerici, M. S., et al. (2014). Increased IL-4 mRNA expression and poly-aromatic hydrocarbon concentrations from children with asthma. *BMC Pediatrics, 14*(1), 17.

Al-Daghri, N. M., Alokail, M. S., Abd-Alrahman, S. H., Draz, H. M., Yakout, S. M., & Clerici, M. (2013). Polycyclic aromatic hydrocarbon exposure and pediatric asthma in children: a case-control study. *Environmental Health, 12,* 1. https://doi.org/10.1186/1476-069X-12-1.

Andreadis, A. A., Hazen, S. L., Comhair, S. A., & Erzurum, S. C. (2003). Oxidative and nitrosative events in asthma. *Free Radical Biology and Medicine, 35*(3), 213–225.

Bakakos, P., Patentalakis, G., & Papi, A. (2016). Vascular biomarkers in asthma and COPD. *Current Topics in Medicinal Chemistry, 16*(14), 1599–1609.

Beasley, R., Semprini, A., & Mitchell, E. A. (2015). Risk factors for asthma: Is prevention possible? *Lancet, 386*(9998), 1075–1085.

Bohm, L., Maxeiner, J., Meyer-Martin, H., Reuter, S., Finotto, S., Klein, M., et al. (2015). IL-10 and regulatory T cells cooperate in allergen-specific immunotherapy to ameliorate allergic asthma. *Journal of Immunology, 194*(3), 887–897.

Bolton, J. L., Trush, M. A., Penning, T. M., Dryhurst, G., & Monks, T. J. (2000). Role of quinones in toxicology. *Chemical Research in Toxicology, 13*(3), 135–160.

Burton, A. (2009). Children's health: Methylation links prenatal PAH exposure to asthma. *Environmental Health Perspectives, 117*(5), A195.

Chang, C. (2013). Unmet needs in respiratory diseases: "You can't know where you are going until you know where you have been"—anonymous. *Clinical Reviews in Allergy and Immunology, 45*(3), 303–313.

Chatzileontiadou, D. S., Parmenopoulou, V., Manta, S., Kantsadi, A. L., Kylindri, P., Griniezaki, M., et al. (2015). Triazole double-headed ribonucleosides as inhibitors of eosinophil derived neurotoxin. *Bioorganic Chemistry, 63,* 152–165.

Chen, Y., Zhang, J., Zhang, F., Li, F., & Zhou, M. (2017). Polycyclic aromatic hydrocarbons in farmland soils around main reservoirs of Jilin Province, China: Occurrence, sources and potential human health risk. *Environmental Geochemistry and Health*. https://doi.org/10.1007/s10653-017-0024-5.

Chinthrajah, R. S., Hernandez, J. D., Boyd, S. D., Galli, S. J., & Nadeau, K. C. (2016). Molecular and cellular mechanisms of food allergy and food tolerance. *The Journal of Allergy and Clinical Immunology, 137*(4), 984–997.

Chu, S., Zhang, H., Maher, C., McDonald, J. D., Zhang, X., Ho, S. M., et al. (2013). Prenatal and postnatal polycyclic aromatic hydrocarbon exposure, airway hyperreactivity, and Beta-2 adrenergic receptor function in sensitized mouse offspring. *Journal of Toxicology, 2013,* 603581. https://doi.org/10.1155/2013/603581.

Ding, J., Li, J., Chen, J., Chen, H., Ouyang, W., Zhang, R., et al. (2006). Effects of polycyclic aromatic hydrocarbons (PAHs) on vascular endothelial growth factor induction through phosphatidylinositol 3-kinase/AP-1-dependent, HIF-1alpha-independent pathway. *Journal of Biological Chemistry, 281*(14), 9093–9100.

Eng, S. S., & DeFelice, M. L. (2016). The role and immunobiology of eosinophils in the respiratory system: A comprehensive review. *Clinical Reviews in Allergy and Immunology, 50*(2), 140–158.

European Respiratory Society. (2013). Adult asthma. In *European Lung White Book*. http://www.erswhitebook.org/chapters/adult-asthma/. Accessed September 06, 2017.

Factor, P., Akhmedov, A. T., McDonald, J. D., Qu, A., Wu, J., Jiang, H., et al. (2011). Polycyclic aromatic hydrocarbons impair function of beta2-adrenergic receptors in airway epithelial and smooth muscle cells. *American Journal of Respiratory Cell and Molecular Biology, 45*(5), 1045–1049.

Feng, X., Lin, J., Su, N., Liu, G., Chen, P., Zhou, X., et al. (2014). Risk factors of bronchial asthma among people aged over 14 years in China. *Zhonghua Yi Xue Za Zhi, 94*(16), 1209–1214.

Gale, S. L., Noth, E. M., Mann, J., Balmes, J., Hammond, S. K., & Tager, I. B. (2012). Polycyclic aromatic hydrocarbon exposure and wheeze in a cohort of children with asthma in Fresno, CA. *Journal of Exposure Science & Environmental Epidemiology, 22*(4), 386–392.

Galowitz, S., & Chang, C. (2015). Immunobiology of critical pediatric asthma. *Clinical Reviews in Allergy and Immunology, 48*(1), 84–96.

Ghosh, R., Rossner, P., Honkova, K., Dostal, M., Sram, R. J., & Hertz-Picciotto, I. (2016). Air pollution and childhood bronchitis: Interaction with xenobiotic, immune regulatory and DNA repair genes. *Environment International, 87,* 94–100.

Ghosh, R., Topinka, J., Joad, J. P., Dostal, M., Sram, R. J., & Hertz-Picciotto, I. (2013). Air pollutants, genes and early childhood acute bronchitis. *Mutation Research, 749*(1–2), 80–86.

Global Asthma Network. (2014). The global asthma report 2014. http://www.globalasthmanetwork.org/publications/Global_Asthma_Report_2014.pdf. Accessed August 23, 2017.

Global Initiative for Asthma. (2018a). Global strategy for asthma management and prevention-online appendix—2018 update. http://ginasthma.org/2018-online-appendix-global-strategy-for-asthma-management-and-prevention/. Accessed June 01, 2018.

Global Initiative for Asthma. (2018b). Global strategy for asthma management and prevention-updated 2018. http://ginasthma.org/2018-online-appendix-global-strategy-for-asthma-management-and-prevention/. Accessed June 01, 2018.

Gosai, H. B., Sachaniya, B. K., Dudhagara, D. R., Rajpara, R. K., & Dave, B. P. (2017). Concentrations, input prediction and probabilistic biological risk assessment of polycyclic aromatic hydrocarbons (PAHs) along Gujarat coastline. *Environmental Geochemistry and Health*. https://doi.org/10.1007/s10653-017-0011-x.

Grainge, C., Thomas, P. S., Mak, J. C., Benton, M. J., Lim, T. K., & Ko, F. W. (2016). Year in review 2015: Asthma and chronic obstructive pulmonary disease. *Respirology, 21*(4), 765–775.

Guo, F. H., Comhair, S. A. A., Zheng, S., Dweik, R. A., Eissa, N. T., Thomassen, M. J., et al. (2000). Molecular mechanisms of increased nitric oxide (NO) in asthma: Evidence for transcriptional and post-translational regulation of NO synthesis. *The Journal of Immunology, 164*(11), 5970–5980.

Guo, Y., Huo, X., Wu, K., Liu, J., Zhang, Y., & Xu, X. (2012). Carcinogenic polycyclic aromatic hydrocarbons in umbilical cord blood of human neonates from Guiyu, China. *Science of the Total Environment, 427–428,* 35–40.

Guo, Y., Wu, K., Huo, X., & Xu, X. (2011). Sources, distribution, and toxicity of polycyclic aromatic hydrocarbons. *Journal of Environmental Health, 73*(9), 22–25.

Harper, R. W., & Zeki, A. A. (2015). Immunobiology of the critical asthma syndrome. *Clinical Reviews in Allergy and Immunology, 48*(1), 54–65.

Hassett, C., Alcher, L., Sidhu, J. S., & Omieclnskl, C. J. (1994). Human microsomal epoxide hydrolase: Genetic poloymorphism and functional expression in vitro of amino acid variants. *Human Molecular Genetics, 3*(3), 421–428.

Hehua, Z., Qing, C., Shanyan, G., Qijun, W., & Yuhong, Z. (2017). The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. *Environmental Research, 159,* 519–530.

Henkler, F., Stolpmann, K., & Luch, A. (2012). Exposure to polycyclic aromatic hydrocarbons: Bulky DNA adducts and cellular responses. *EXS, 101,* 107–131.

Hew, K. M., Walker, A. I., Kohli, A., Garcia, M., Syed, A., McDonald-Hyman, C., et al. (2015). Childhood exposure to ambient polycyclic aromatic hydrocarbons is linked to epigenetic modifications and impaired systemic immunity in T cells. *Clinical and Experimental Allergy, 45*(1), 238–248.

Hong, C. H., Lee, C. H., Yu, H. S., & Huang, S. K. (2016). Benzopyrene, a major polyaromatic hydrocarbon in smoke fume, mobilizes Langerhans cells and polarizes Th2/17 responses in epicutaneous protein sensitization through the aryl hydrocarbon receptor. *International Immunopharmacology, 36,* 111–117.

Iarmarcovai, G., Bonassi, S., Botta, A., Baan, R. A., & Orsiere, T. (2008). Genetic polymorphisms and micronucleus formation: A review of the literature. *Mutation Research, 658*(3), 215–233.

International Programme on Chemical Safety. (1998). No. 202—polycyclic aromatic hydro-carbons, selected non-heterocyclic (1998)—full text [htm]. http://www.inchem.org/documents/ehc/ehc/ehc202.htm. Accessed September 02, 2017.

Jansen, D. F., Rijcken, B., Schouten, J. P., Kraan, J., Weiss, S. T., Timens, W., et al. (1999). The relationship of skin test positivity, high serum total IgE levels, and peripheral blood eosinophilia to symptomatic and asymptomatic airway hyperresponsiveness. *American Journal of Respiratory and Critical Care Medicine, 159*(3), 924–931.

Jedrychowski, W., Galas, A., Pac, A., Flak, E., Camman, D., Rauh, V., et al. (2005). Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life. *European Journal of Epidemiology, 20*(9), 775–782.

Jedrychowski, W. A., Perera, F. P., Majewska, R., Camman, D., Spengler, J. D., Mroz, E., et al. (2014). Separate and joint effects of tranplacental and postnatal inhalatory exposure to polycyclic aromatic hydrocarbons: prospective birth cohort study on wheezing events. *Pediatric Pulmonology, 49*(2), 162–172.

Jung, K. H., Perzanowski, M., Rundle, A., Moors, K., Yan, B., Chillrud, S. N., et al. (2014). Polycyclic aromatic

hydrocarbon exposure, obesity and childhood asthma in an urban cohort. *Environmental Research, 128,* 35–41.

Jung, K. H., Yan, B., Moors, K., Chillrud, S. N., Perzanowski, M. S., Whyatt, R. M., et al. (2012). Repeated exposure to polycyclic aromatic hydrocarbons and asthma: effect of seroatopy. *Annals of Allergy, Asthma & Immunology, 109*(4), 249–254.

Karimi, P., Peters, K. O., Bidad, K., & Strickland, P. T. (2015). Polycyclic aromatic hydrocarbons and childhood asthma. *European Journal of Epidemiology, 30*(2), 91–101.

Keshavarzifard, M., Moore, F., Keshavarzi, B., & Sharifi, R. (2017). Distribution, source apportionment and health risk assessment of polycyclic aromatic hydrocarbons (PAHs) in intertidal sediment of Asaluyeh, Persian Gulf. *Environmental Geochemistry and Health*. https://doi.org/10.1007/s10653-017-0019-2.

Kim, S. R., Lee, K. S., Park, S. J., Min, K. H., Choe, Y. H., Moon, H., et al. (2010). Involvement of sirtuin 1 in airway inflammation and hyperresponsiveness of allergic airway disease. *The Journal of Allergy and Clinical Immunology, 125*(2), 449–460 e414.

Kudo, M., Ishigatsubo, Y., & Aoki, I. (2013). Pathology of asthma. *Frontiers in Microbiology, 4,* 263. https://doi.org/10.3389/fmicb.2013.00263.

Lee, J. U., Kim, J. D., & Park, C. S. (2015). Gene-environment interactions in asthma: Genetic and epigenetic effects. *Yonsei Medical Journal, 56*(4), 877–886.

Lee, J., Nordestgaard, B. G., & Dahl, M. (2011). EPHX1 polymorphisms, COPD and asthma in 47,000 individuals and in meta-analysis. *European Respiratory Journal, 37*(1), 18–25.

Li, Z., Romanoff, L., Bartell, S., Pittman, E. N., Trinidad, D. A., McClean, M., et al. (2012). Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chemical Research in Toxicology, 25*(7), 1452–1461.

Liu, H., Xu, C., Jiang, Z. Y., & Gu, A. (2016). Association of polycyclic aromatic hydrocarbons and asthma among children 6–19 years: NHANES 2001–2008 and NHANES 2011–2012. *Respiratory Medicine, 110,* 20–27.

Lubitz, S., Schober, W., Pusch, G., Effner, R., Klopp, N., Behrendt, H., et al. (2010). Polycyclic aromatic hydrocarbons from diesel emissions exert proallergic effects in birch pollen allergic individuals through enhanced mediator release from basophils. *Environmental Toxicology, 25*(2), 188–197.

Martinez-Giron, R., & Martinez-Torre, C. (2016). Cytolytic degranulation of eosinophils in sputum smears. *Diagnostic Cytopathology, 44*(3), 220–222.

McCoull, K. D., Rindgen, D., Blair, I. A., & Penning, T. M. (1999). Synthesis and characterization of polycyclic aromatic hydrocarbon o-quinone depurinating N7-guanine adducts. *Chemical Research in Toxicology, 12*(3), 237–246.

Miller, R. L., Garfinkel, R., Lendor, C., Hoepner, L., Li, Z., Romanoff, L., et al. (2010). Polycyclic aromatic hydrocarbon metabolite levels and pediatric allergy and asthma in an inner-city cohort. *Pediatric Allergy and Immunology, 21*(2 Pt 1), 260–267.

Miller, M., Vuong, C., Garcia, M. F., Rosenthal, P., Das, S., Weng, N., et al. (2018). Does reduced zona pellucida binding protein 2 (ZPBP2) expression on chromosome 17q21 protect against asthma? *The Journal of Allergy and Clinical Immunology, 142*(2), 706–709.e4.

Modena, B. D., Dazy, K., & White, A. A. (2016). Emerging concepts: mast cell involvement in allergic diseases. *Translational Research, 174,* 98–121.

Moorman, J. E., Akinbami, L. J., Bailey, C. M., Zahran, H. S., King, M. E., Johnson, C. A., et al. (2012). National surveillance of asthma: United States, 2001–2010. *Vital & Health Statistics 3, 35*(35), 1–58.

Morgan, R. K., Costello, R. W., Durcan, N., Kingham, P. J., Gleich, G. J., McLean, W. G., et al. (2005). Diverse effects of eosinophil cationic granule proteins on IMR-32 nerve cell signaling and survival. *American Journal of Respiratory Cell and Molecular Biology, 33*(2), 169–177.

NCBI. (2017). EPHX1 epoxide hydrolase 1, microsomal (xenobiotic) [Homo sapiens (human)]. NCBI. http://www.ncbi.nlm.nih.gov/gene/2052. Accessed September 06, 2017.

NCBI (2018a). Reference SNP (refSNP) Cluster Report: rs1051740. NCBI. https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1051740. Accessed August 16, 2018.

NCBI (2018b). Reference SNP (refSNP) Cluster Report: rs2234922. NCBI. https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2234922. Accessed August 16, 2018.

Nel, A. E., Diaz-Sanchez, D., & Li, N. (2001). The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. *Current Opinion in Pulmonary Medicine, 7*(1), 20–26.

Nel, A. E., Diaz-Sanchez, D., Ng, D., Hiura, T., & Saxon, A. (1998). Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *The Journal of Allergy and Clinical Immunology, 102*(4 Pt 1), 539–554.

Papi, A., Brightling, C., Pedersen, S. E., & Reddel, H. K. (2018). Asthma. *The Lancet, 391,* 783–800.

Peluso, M. E., Munnia, A., Srivatanakul, P., Jedpiyawongse, A., Sangrajrang, S., Ceppi, M., et al. (2013). DNA adducts and combinations of multiple lung cancer at-risk alleles in environmentally exposed and smoking subjects. *Environmental and Molecular Mutagenesis, 54*(6), 375–383.

Ple, C., Fan, Y., Ait Yahia, S., Vorng, H., Everaere, L., Chenivesse, C., et al. (2015). Polycyclic aromatic hydrocarbons reciprocally regulate IL-22 and IL-17 cytokines in peripheral blood mononuclear cells from both healthy and asthmatic subjects. *PLoS ONE, 10*(4), e0122372. https://doi.org/10.1371/journal.pone.0122372.

Postma, D. S., Weiss, S. T., van den Berge, M., Kerstjens, H. A., & Koppelman, G. H. (2015). Revisiting the Dutch hypothesis. *The Journal of Allergy and Clinical Immunology, 136*(3), 521–529.

Qu, C., Li, B., Wu, H., Wang, S., & Giesy, J. P. (2015). Multipathway assessment of human health risk posed by polycyclic aromatic hydrocarbons. *Environmental Geochemistry and Health, 37*(3), 587–601.

Ravin, K. A., & Loy, M. (2016). The eosinophil in infection. *Clinical Reviews in Allergy and Immunology, 50*(2), 214–227.

Ren, Y., Ichinose, T., He, M., Arashidani, K., Yoshida, Y., Yoshida, S., et al. (2014). Aggravation of ovalbumin-

induced murine asthma by co-exposure to desert-dust and organic chemicals: An animal model study. *Environmental Health, 13,* 83. https://doi.org/10.1186/1476-069X-13-83.

Repine, J. E., Bast, A., Lankhorst, I., & Group, T. O. S. S. (1997). Oxidative stress in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 156,* 341–357.

Salam, M. T., Lin, P. C., Avol, E. L., Gauderman, W. J., & Gilliland, F. D. (2007). Microsomal epoxide hydrolase, glutathione S-transferase P1, traffic and childhood asthma. *Thorax, 62*(12), 1050–1057.

Sha, L., Shao, M., Liu, C., Li, S., Li, Z., Luo, Y., et al. (2015). The prevalence of asthma in children: a comparison between the year of 2010 and 2000 in urban China. *Zhonghua Jie He He Hu Xi Za Zhi, 38*(9), 664–668.

Smargiassi, A., Goldberg, M. S., Wheeler, A. J., Plante, C., Valois, M. F., Mallach, G., et al. (2014). Associations between personal exposure to air pollutants and lung function tests and cardiovascular indices among children with asthma living near an industrial complex and petroleum refineries. *Environmental Research, 132,* 38–45.

Sram, R. J., Binkova, B., Dostal, M., Merkerova-Dostalova, M., Libalova, H., Milcova, A., et al. (2013). Health impact of air pollution to children. *International Journal of Hygiene and Environmental Health, 216*(5), 533–540.

Stevens, T., Cho, S. H., Linak, W. P., & Gilmour, M. I. (2009). Differential potentiation of allergic lung disease in mice exposed to chemically distinct diesel samples. *Toxicological Sciences, 107*(2), 522–534.

Stiborova, M., Moserova, M., Cerna, V., Indra, R., Dracinsky, M., Sulc, M., et al. (2014). Cytochrome b5 and epoxide hydrolase contribute to benzo[a]pyrene-DNA adduct formation catalyzed by cytochrome P450 1A1 under low NADPH:P450 oxidoreductase conditions. *Toxicology, 318,* 1–12.

Sunyer, J., & Munoz, A. (1996). Concentrations of methacholine for bronchial responsiveness according to symptoms, smoking and immunoglobulin E in a population-based study in Spain. Spanish Group of the European Asthma Study. *American Journal of Respiratory and Critical Care Medicine, 153*(4 Pt 1), 1273–1279.

Tang, W. Y., Levin, L., Talaska, G., Cheung, Y. Y., Herbstman, J., Tang, D., et al. (2012). Maternal exposure to polycyclic aromatic hydrocarbons and 5'-CpG methylation of interferon-γ in cord white blood cells. *Environmental Health Perspectives, 120*(8), 1195–1200.

Toldi, G., Molvarec, A., Stenczer, B., Muller, V., Eszes, N., Bohacs, A., et al. (2011). Peripheral T(h)1/T(h)2/T(h)17/regulatory T-cell balance in asthmatic pregnancy. *International Immunology, 23*(11), 669–677.

Torgerson, D. G., Ampleford, E. J., Chiu, G. Y., Gauderman, W. J., Gignoux, C. R., Graves, P. E., et al. (2011). Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nature Genetics, 43*(9), 887–892.

Trifari, S., Kaplan, C. D., Tran, E. H., Crellin, N. K., & Spits, H. (2009). Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. *Nature Immunology, 10*(8), 864–871.

Tung, K. Y., Tsai, C. H., & Lee, Y. L. (2011). Microsomal epoxide hydroxylase genotypes/diplotypes, traffic air pollution, and childhood asthma. *Chest, 139*(4), 839–848.

Vaclavikova, R., Hughes, D. J., & Soucek, P. (2015). Microsomal epoxide hydrolase 1 (EPHX1): Gene, structure, function, and role in human disease. *Gene, 571*(1), 1–8.

van Voorhis, M., Knopp, S., Julliard, W., Fechner, J. H., Zhang, X., Schauer, J. J., et al. (2013). Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor. *PLoS ONE, 8*(12), e82545. https://doi.org/10.1371/journal.pone.0082545.

Verma, A. H., Bueter, C. L., Rothenberg, M. E., & Deepe, G. S. (2017). Eosinophils subvert host resistance to an intracellular pathogen by instigating non-protective IL-4 in $CCR2^{-/-}$ mice. *Mucosal Immunology, 10*(1), 194–204.

Wandalsen, G. F., Sole, D., & Bacharier, L. B. (2016). Identification of infants and preschool children at risk for asthma: Predictive scores and biomarkers. *Current opinion in Allergy and Clinical Immunology, 16*(2), 120–126.

Wang, I. J., & Karmaus, W. J. (2017). Oxidative stress-related genetic variants may modify associations of phthalate exposures with asthma. *International Journal of Environmental Research and Public Health, 14*(2), 162.

Wang, I. J., Karmaus, W. J., & Yang, C. C. (2017). Polycyclic aromatic hydrocarbons exposure, oxidative stress, and asthma in children. *International Archives of Occupational and Environmental Health, 90*(3), 297–303.

Wilkerson, E. M., Johansson, M. W., Hebert, A. S., Westphall, M. S., Mathur, S. K., Jarjour, N. N., et al. (2016). The peripheral blood eosinophil proteome. *Journal of Proteome Research, 15*(5), 1524–1533.

World Allergy Organization (2013). WAO white book on allergy 2013 update. http://www.worldallergy.org/UserFiles/file/ExecSummary-2013-v6-hires.pdf. Accessed September 06, 2017.

World Health Organization, Regional Office for Europe (2010). WHO guideline for indoorair quality: Selected pollutants. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf?ua=1. Accessed September 01, 2017.

Xia, G. L., Wang, Y. K., & Huang, Z. Q. (2016). The correlation of serum myeloid-related protein-8/14 and eosinophil cationic protein in patients with coronary artery disease. *BioMed Research International, 2016,* 4980251. https://doi.org/10.1155/2016/4980251.

Xiang, M., Ao, L., Yang, H., Liu, W., Sun, L., Han, X., et al. (2012). Chromosomal damage and polymorphisms of metabolic genes among 1, 3-butadiene-exposed workers in a matched study in China. *Mutagenesis, 27*(4), 415–421.

Xu, H., Guinot, B., Ho, S. S. H., Li, Y., Cao, J., Shen, Z., et al. (2017). Evaluation on exposures to particulate matter at a junior secondary school: A comprehensive study on health risks and effective inflammatory responses in Northwestern China. *Environmental Geochemistry and Health*. https://doi.org/10.1007/s10653-017-0030-7.

Xu, X., Liu, J., Huang, C., Lu, F., Chiung, Y. M., & Huo, X. (2015). Association of polycyclic aromatic hydrocarbons (PAHs) and lead co-exposure with child physical growth and development in an e-waste recycling town. *Chemosphere, 139,* 295–302.

Zakharenko, A. M., Engin, A. B., Chernyshev, V. V., Chaika, V. V., Ugay, S. M., Rezaee, R., et al. (2017). Basophil

mediated pro-allergic inflammation in vehicle-emitted particles exposure. *Environmental Research, 152,* 308–314.

Zhang, S., Li, G., Tian, L., Guo, Q., & Pan, X. (2016). Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: A systematic review and meta-analysis. *Environmental Research, 148,* 15–23.

Zhou, Y., Sun, H., Xie, J., Song, Y., Liu, Y., Huang, X., et al. (2016). Urinary polycyclic aromatic hydrocarbon metabolites and altered lung function in Wuhan, China. *American Journal of Respiratory and Critical Care Medicine, 193*(8), 835–846.

Zhou, Y., Tung, H. Y., Tsai, Y. M., Hsu, S. C., Chang, H. W., Kawasaki, H., et al. (2013). Aryl hydrocarbon receptor controls murine mast cell homeostasis. *Blood, 121*(16), 3195–3204.

Zuo, L., Otenbaker, N. P., Rose, B. A., & Salisbury, K. S. (2013). Molecular mechanisms of reactive oxygen species-related pulmonary inflammation and asthma. *Molecular Immunology, 56*(1–2), 57–63.