

## **Roll of Air Pollution on Pathogenesis of Asthma and Allergic Diseases: Review article**

### **Abstract**

**Background:** Air pollution is one of the prevalent causes of in the pathogenesis of respiratory disorders. The main air pollutants are NO<sub>x</sub>, SO<sub>x</sub> and O<sub>3</sub> that affects quality of life and health. Therefore, assessment of air pollutants effects on the pathogenesis of asthma and allergic diseases may leads to better this quality and reduce the prevalence of the diseases.

**Methods:** The sample size of this study were the articles indexed in and contained the terms" Air pollution, Asthma, Allergy". In this research, 86 articles with the keywords were found in the databases mentioned above. From these articles, 55 articles for writing of this review were used.

**Results:** Air pollutants induced nonspecific immune and allergic inflammation with enhances production of IL-4, IL-5, and IL-13 by Th2 lymphocytes. And, original articles reported that there is significant relationship between air pollution and asthma and allergic diseases. Therefore, air pollution has role in the pathogenesis and exacerbation of the diseases.

**Key words:** Air pollution, Asthma and Allergic diseases, Allergic inflammation

### **Introduction**

Air pollution is one of the main causes of pulmonary disease in developed countries especially in large cities. These days, air pollution is a general health problem which has adverse effect on the quality of life specially in large cities and cities with high traffic rate(1). Air pollution sources are biogenic sources such as volcanic activities, natural fire, desert dust and human activities (Anthropogenic sources). Other air pollution sources related to human's activity are divided into two categories which are motile and immotile sources. Motile sources include motor vehicle exhaust gases, and immotile sources are home appliances using fuel, industrial facilities and power stations(1, 2). Generally, outdoor pollutants are two types: primary contaminants such as carbon monoxide (CO) of vehicles exhaust or sulfur dioxide (SO<sub>2</sub>) which enter to environment from industrial activities. Secondary pollutants are ones which are produced as result of chemical

activities on primary contaminants in atmosphere. These kinds of pollutants are produced from sunrays and air humidity. For example, Ozone (O<sub>3</sub>) is produced from effect of sunrays on volatile Hydrocarbons or secondary micro particles in the atmosphere such as sulfates. The result of all these processes is production of gases like ozone (O<sub>3</sub>), carbon monoxide (CO), carbon dioxide (CO<sub>2</sub>), nitrogen monoxide (NO), nitrogen dioxide (NO<sub>2</sub>), nitrogen trioxide (NO<sub>3</sub>), sulfur dioxide (SO<sub>2</sub>) and all other micro particles (PM<sub>0.1</sub> .PM<sub>2.5</sub> .PM<sub>10</sub>) which are floating in air(3, 4). Air pollution caused by car traffic in many cities and specially in urban areas is a giant source of air pollution which include Benzene from lead-free diesel, organic chemical material released from diesel exhaust, NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub> as actuator gases and PM(2). In addition, due to fuel evaporation and ray emissions from motor vehicle exhausts mixture of CO, PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>3</sub>, hydrocarbons and ozone are introduced inside outdoor air. NO, NO<sub>2</sub> and NO<sub>3</sub> are pollutants of the air which are mainly produced from diesel engines and fuel based machines in power stations or factories which run by coal or oil(2). Among these gases, NO and NO<sub>2</sub> play an important role in air pollution because of their heavy destructive effect on human health(3, 4). Ozone (O<sub>3</sub>) is a very active gas which is produced primarily in result of effect of sun light on hydrocarbons and NO<sub>x</sub> which are produced from burning of fossil fuels(2). Exposure to ozone gas in animal model can cause toxicity during fetal development period(5). CO is a primary pollutant which competitively inhibits oxygen (O<sub>2</sub>) transport by binding to hemoglobin and producing carboxyhemoglobin(6). Co gas is mainly produced from normal transports by vehicles in big cities(7). SO<sub>2</sub> is another example of primary pollutants which is harmful for humans and environment(8). This gas is produced from oxidation of sulfur of fuel or from industrial activities which sulfur components are used in(5, 9, 10). So, thermal power planets are the main sources of production of SO<sub>2</sub> compare to other industries in IRAN(11). PM are composed of solid particle and liquid micro particles of chemical compositions and physical particles which are suspended in air due to their low aerodynamic diameter are divided into Fine and Ultrafine(2). Lead as one of the air pollutants is mostly exposed to children with soil and materials use for painting(12, 13). Industrial sources like battery making factories and metal melting stations introduce huge amount of lead to environment(14). In some areas where lead included diesel is still used, vehicles in traffic enter huge amount of lead into air(15). The most important source of lead contamination is air dust(16). Studies in some US institution centers, showed 18 percent of children aged between 1 to 5 had been polluted by lead which in 6.6 percent of them, the amount

was toxic(9). Other study (1988-1994) in England and USA on children aged between 1-5 and Iran(province: Semnan) took place and the amount of lead pollution was reported 8.6, 6.3, 8.7 percent respectively(11, 17, 18) .

## **Research method**

The articles used to prepare and write this article can be found in international and national article research centers; including, pub med, Elsevier, Trip database, Embase, Black Cochrane, New spring link, Ovid, SID by searching keywords “Air pollution, Asthma, Allergy”. 86 articles had been studied which 57 of them are used to write this review article.

## **Studies review**

According to studies on asthma immunopathology, approximately 70 percent of atopic asthma cases are associated with rapid reaction of IgE with allergens. In remaining 30 percent may also occur due to non-immunological stimuli such as medications, cold temperature and exercise. Asthma, a chronic inflammatory disease, occurs as a result of the activation of mast cells in response to the allergen binding to IgE and is affected by the response to Th2 contributing T cell. It has been empirically proven that other subunits cells like Th1, Th17 and also involvement of IL-9 cytokine secreted from T-cell play an important role in inflammation. In addition, mast cells, basophils and eosinophils produce all of mediators, such as LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub> which all are leukotrienes, Which they can cause contraction of smooth muscles in respiratory tract(19).

Air pollution caused by dust which occurs in east and west Asia can be source to accentuate asthma symptoms. It seems like factors and mineral elements like SiO<sub>2</sub> which is the main component of soil particles in Asia, stimulates secretion of cytokines of Th2 cells(IL-4, IL-5, IL-13) . The result of a study showed that increase in serum levels of IL-4 and IL-3 in individuals which are under exposure of air dust may stimulate B cells which causes production of IgE antibody for specific antigens and also exacerbates allergic inflammation. Content of air dust in western states of Iran are microorganisms, pollen of plants, trees and fungi(20-22).

In a study done in Iran (province: Bushehr), it is reported that the number of B-lymphocytes(CD19+) and T- lymphocytes (CD4+and CD25+) in individuals which are exposed to air dust pollution has been significantly increased(23).

In recent years, epidemiologic studies showed prevalence of allergic disease in children and adolescents is increasing(24-26). children, elders and individuals with some specific disease like asthma are more affected by air pollution. As children spend more time in outdoor compare to adults, so they inhale more volume of polluted air per pound of body weight. A study in Europe reported that air pollution is significantly associated with the number of B-cells, CD 4+ and CD8+ T-cells, NK cells during childhood ages(27).

Another study showed that exposure to aromatic hydrocarbons such as Polycyclic Aromatic Hydrocarbons (PAH), PM<sub>2.5</sub>during the last two weeks of pregnancy significantly increased the number of B cell lymphocytes and decrease the number of T cell lymphocytes in placenta and umbilical cord(28). According to WHO report in 2008, air pollutions in cities was responsible for annual death of 13 million people(29). Also some evidences showed air pollution caused by traffic in cities plays important role in prevalence of asthma(30, 31). In addition, recent epidemiologic studies have shown that Asian dust can worsen allergic diseases such as asthma(32-34). It was also showed in a experimental study that rats had bronchial and pulmonary inflammation after frequent exposure to Asian dust.

This means that Asian dust causes increase number of neutrophils by chemokines and cytokines such as IL -12, IL -1 b, TNF- $\alpha$ , IL -6, IL -12, IL -17A in air ways which can be proven in Broncho alveolar Lavage Fluid (BALF)(20). Also pollutants such as exhaust particles from diesel engines may have synergistic effects with allergens in upper respiratory tract mucoid tissue, which increases production of specific IgE of the allergen following increase in Th2 dependent cytokines(6). During a study which done by Ozcan and Cubukcu in 2012, they found out between years 2007-2010, in Turkey(Province: Izmir), there was a significant relation between number of individuals suffering from asthma and urban air pollution level which was due to high volume of SO<sub>2</sub>, PM<sub>10</sub>(14). In other study, voluntaries were subjected to a diesel exhaust particle (DEP) for an hour. The Experiments showed increase in number of peripheral blood mononuclear cell and increase of vascular cell adhesion

molecules (VCAM-1) and epithelial cell adhesion molecule in lungs tissue. Also in adults, elevated C-reactive protein (CRP) level and markers for acute inflammation can be observed after exposure to air pollution(6, 9, 15, 16, 18-38). Based on studies done in Netherland, Uk and Italy, elevated incidence of wheezing, chronic cough and asthma can be seen more in urban areas. In fact, diesel engines exhaust gases, can increase inflammatory response followed by increase in sensitivity to antigenic agents(30, 31, 39-50). Due to variation in air pollutants, various effects have been reported, so that in Sweden there is a strong connection between asthma exacerbation, and increased NO<sub>2</sub> in air in the same day(51). Also large amount of NO<sub>2</sub> in air was associated with increase in the number of patients in emergency department For asthma during summer and winter in Spain(Barcelona)(52). Based on studies in Paris, there was strongest connection between asthma exacerbation and increased sulfur dioxide on the same days(53). Also recent studies on asthmatic patients in 12 hospital in London reported that the main reason of referring these patients to hospital is significant increase in level of NO<sub>2</sub> and SO<sub>2</sub> in air(54). In addition, many reports indicated increase in respiratory disease symptoms in children is due to exposure to NO<sub>2</sub> resulting from gas oven in kitchens(55).

Epidemiologic and clinical studies showed that O<sub>3</sub> radiation is associated with impairment athletes performance decrease lungs function, decrease respiration, chest pain with deep inhalation, wheezing, cough and asthma exacerbation(56). Since 2005, approximately 35 million people have lost their lives during next 10 years (until 2015) due to chronic pulmonary disease such as asthma and chronic obstructive pulmonary disease (COPD) in all around the world and mortality rate due to these chronic diseases has increased 17 percent in Turkey. According to this fact, all these studies and reports are referring to relationship between air pollution with the development and exacerbation of asthma and allergic diseases(57).

## **Conclusion**

Various epidemiological studies have shown that air pollution exacerbates pulmonary disease in human beings. Many of these contaminants having oxidant effect cause and exacerbate respiratory tract inflammation. It has also been suggested that air pollution will change the type of response to allergens and in response increase the sensitivity to these allergens. In fact this type of immunological response, responds to the stimulation Th<sub>2</sub> lymphocytes and increase the

production of IL-4, IL-5, IL-13 and cytokines by these cells. Therefore, air pollution plays an important role in stimulation of symptoms of asthma and allergy.

### **Acknowledgements**

This study was financially supported by Vice-Chancellery Research & Technology Affairs of Bushehr University of Medical Sciences.

### **References**

1. Franchini M, Guida A, Tufano A, Coppola A. Air pollution, vascular disease and thrombosis: linking clinical data and pathogenic mechanisms. *J Thromb Haemost*. 2012;10(12):14.
2. Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. *Journal of allergy and clinical immunology*. 2005;115(4):11.
3. Murathan A, Biçer A, Alicilar A, Murathan A. Effects of various parameters on removal of NO<sub>2</sub> gases in fixed beds by adsorption on sepiolite. *Water, Air, and Soil Pollution*. 2003;139(1-4):1-10.
4. Murray F, McGranahan G. Air pollution and health in rapidly developing countries-the context. 2003.
5. Kavlock R, Daston G, Grabowski CT. Studies on the developmental toxicity of ozone. I. Prenatal effects. *Toxicology and applied pharmacology*. 1979;48(1):10.
6. Bastain TM, Gilliland FD, Li Y-F, Saxon A, Diaz-Sanchez D. Intraindividual reproducibility of nasal allergic responses to diesel exhaust particles indicates a susceptible phenotype. *Clinical Immunology*. 2003;109(2):7.
7. Peters A, von Klot S, Heier M, Group CHRitRoAS. Exposure to traffic and the onset of myocardial infarction. *ACC Current Journal Review*. 2005;14(1):19.
8. CRIES C, Sanz MJ, Romagni JG, Goldsmith S, Kuhn U, Kesselmeier J, et al. The uptake of gaseous sulphur dioxide by non-gelatinous lichens. *New phytologist*. 1997;135(4):8.
9. Koren HS, Devlin RB, Graham DE, Mann R, McGee MP, Horstman DH, et al. Ozone-induced inflammation in the lower airways of human subjects. *American review of respiratory disease*. 1989;139(2):9.
10. McGranahan G, Murray F. Air pollution and health in rapidly developing countries: Earthscan; 2012.
11. Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma: A paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clinical Immunology*. 2003;109(3):250-65.
12. Hajat S, Haines A, Goubet S, Atkinson R, Anderson H. Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. *Thorax*. 1999;54(7):9.
13. Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. *Environmental Research*. 1997;74(1):7.

- .۱۴ Ozcan NS, Cubukcu KM. Evaluation of Air Pollution Effects on Asthma Disease: The case of Izmir. *Procedia-Social and Behavioral Sciences*. 2۰۲۰;۸۰۱۰
- .۱۵ Pryor W, Church D. The reaction of ozone with unsaturated fatty acids: aldehydes and hydrogen peroxide as mediators of ozone toxicity. *Oxidative Damage & Repair: Chemical, Biological and Medical Aspects*. 1991:9.
- .۱۶ Mendelsohn AL, Dreyer BP, Fierman AH, Rosen CM, Legano LA, Kruger HA, et al. Low-level lead exposure and cognitive development in early childhood. *Journal of Developmental & Behavioral Pediatrics*. 1999;20(6):7.
- .۱۷ Benjamin J, Platt C. Is universal screening for lead in children indicated? An analysis of lead results in Augusta, Georgia in 1997. *Journal of the Medical Association of Georgia*. ۱۹۹۹;۸۸(۴):۳.
- .۱۸ Kaufmann RB, Clouse TL, Olson DR, Matte TD. Elevated blood lead levels and blood lead screening among US children aged one to five years: 1988–1994. *Pediatrics*. 2000;106(6).
- .۱۹ Abbas AK, Lichtman AH, Pillai S. *Cellular and molecular immunology: Elsevier Health Sciences*; 2014.
- .۲۰ He M, Ichinose T, Yoshida S, Takano H, Nishikawa M, Sun G, et al. Induction of immune tolerance and reduction of aggravated lung eosinophilia by co-exposure to Asian sand dust and ovalbumin for 14 weeks in mice. *Allergy Asthma Clin Immunol*. 2013;9(19):9.
- .۲۱ Hiyoshi K, Ichinose T, Sadakane K, Takano H, Nishikawa M, Mori I, et al. Asian sand dust enhances ovalbumin-induced eosinophil recruitment in the alveoli and airway of mice. *Environmental research*. 2005;99(3):8
- .۲۲ Shahsavani A, Naddafi K, Haghhighifard NJ, Mesdaghinia A, Yunesian M, Nabizadeh R, et al. Characterization of ionic composition of TSP and PM10 during the Middle Eastern Dust (MED) storms in Ahvaz, Iran. *Environmental monitoring and assessment*. 2012;184(11):10.
- .۲۳ Gheybi MK, Movahed A, Dehdari R, Amiri S, Khazaei HA, Gooya M, et al. Dusty Air Pollution is Associated with an Increased Risk of Allergic Diseases in Southwestern Part of Iran. *Iranian Journal of Allergy, Asthma and Immunology*. 2014;13(6).
- .۲۴ Ghazi BM, Imamzadehgan R, Aghamohammadi A, Darakhshavari R, Rezaei N. Frequency of allergic rhinitis in school-age children (7-18 years) in Tehran. *Iranian Journal of allergy, asthma and Immunology*. 2003;2(4):4.
- .۲۵ Shakurnia A, Assar S, Afra M, Latifi M. Prevalence of asthma among schoolchildren in Ahvaz, Islamic Republic of Iran/Prévalence de l'asthme chez les élèves d'Ahvaz (République islamique d'Iran). *Eastern Mediterranean Health Journal*. 2010;16(6).
- .۲۶ Zobeiri M. Prevalence, risk factors and severity of asthma symptoms in children of Kermanshah, IRAN: ISAAC phase I, II. *Acta Medica Iranica*. 2011;49(3).
- .۲۷ Leonardi G, Houthuijs D, Steerenberg P, Fletcher T, Armstrong B, Antova T, et al. Immune biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of Central Europe. *Inhalation toxicology*. 2000;12(sup4):14.
- .۲۸ Hertz-Picciotto I, Herr CE, Yap P-S, Dostál M, Shumway RH, Ashwood P, et al. Air pollution and lymphocyte phenotype proportions in cord blood. *Environmental health perspectives*. 2005:8.

- .۲۹ Cloutier MM, Wakefield DB, Hall CB, Bailit HL. Childhood Asthma in an Urban Community\*: Prevalence, Care System, and Treatment. *Journal of Chest* 2002;122(2):1571-9.
- .۳۰ McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, et al. Asthma in exercising children exposed to ozone: a cohort study. *The Lancet*. 2002;359(9304):6.
- .۳۱ McDonnell WF, Abbey DE, Nishino N, Lebowitz MD. Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study. *Environmental Research*. 1999;80(2):12.
- .۳۲ Chang C-C, Chen C-Y, Chiu H-F, Dai S-X, Liu M-Y, Yang C-Y. Elastases from inflammatory and dendritic cells mediate ultrafine carbon black induced acute lung destruction in mice. *Inhalation toxicology*. 2011;23(10):11.
- .۳۳ Chang C-C, Lee I-M, Tsai S-S, Yang C-Y. Correlation of Asian dust storm events with daily clinic visits for allergic rhinitis in Taipei, Taiwan. *Journal of Toxicology and Environmental Health, Part A*. 2006;69(3):7.
- .۳۴ Otani S, Onishi K, Mu H, Yokoyama Y, Hosoda T, Okamoto M, et al. The relationship between skin symptoms and allergic reactions to Asian dust. *International journal of environmental research and public health*. 2012;9(12):9.
- .۳۵ Bernstein JA, Alexis N, Barnes C, Bernstein IL, Nel A, Peden D, et al. Health effects of air pollution. *Journal of allergy and clinical immunology*. 2004;11.^(۵)۴
- .۳۶ Mudway IS, Krishna MT, Frew AJ, MacLeod D, Sandstrom T, Holgate ST, et al. Compromised concentrations of ascorbate in fluid lining the respiratory tract in human subjects after exposure to ozone. *Occupational and environmental medicine*. 1999;5.۹:(۷)۶
- .۳۷ Otani S, Onishi K, Mu H, Kurozawa Y. The effect of Asian dust events on the daily symptoms in Yonago, Japan: a pilot study on healthy subjects. *Archives of environmental & occupational health*. 2011;66(1):4.
- .۳۸ Saintot M, Bernard N, Astre C, Gerber M, Inserm-crlc. Ozone exposure and blood antioxidants: a study in a periurban area in Southern France. *Archives of Environmental Health: An International Journal*. 1999;54(1):6.
- .۳۹ Berkowitz GS, Wolff MS, Janevic TM, Holzman IR, Yehuda R, Landrigan PJ. The World Trade Center disaster and intrauterine growth restriction. *Jama*. 2003;290(5):2.
- .۴۰ Bornschein RL, Succop P, Krafft K, Clark C, Peace B, Hammond P. Exterior surface dust lead, interior house dust lead and childhood lead exposure in an urban environment. *Univ. of Cincinnati, OH*; 1986.
- .۴۱ Diaz-Sanchez D, Garcia MP, Wang M, Jyrala M, Saxon A. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. *Journal of allergy and clinical immunology*. ۶:(۶)۱۰۴;۱۹۹۹ .
- .۴۲ Duggan MJ, Inskip M. Childhood exposure to lead in surface dust and soil: a community health problem. *Public Health Reviews*. 1984;13(1-2):55.
- .۴۳ Landrigan PJ, Lioy PJ, Thurston G, Berkowitz G, Chen L, Chillrud SN, et al. Health and environmental consequences of the world trade center disaster. *Environmental health perspectives*. 2004;112(6.(
- .۴۴ Lanphear BP, Matte TD, Rogers J, Clickner RP, Dietz B, Bornschein RL, et al. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: a pooled analysis of 12 epidemiologic studies. *Environmental research*. 1998;79(1):18.

.٤٥ Nel AE, Diaz-Sanchez D, Ng D, Hiura T, Saxon A. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *Journal of Allergy and Clinical Immunology*. 1998;102(4):16.

.٤٦ Peden DB, Setzer Jr RW, Devlin RB. Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics. *American journal of respiratory and critical care medicine*. ١٩٩٥;١٥١(٥):١٠.

.٤٧ Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. Air pollution from traffic at the residence of children with cancer. *American journal of epidemiology*. 2001;153(5):11

.٤٨ Saldiva PH, Lichtenfels A, Paiva P, Barone I, Martins M, Massad E, et al. Association between air pollution and mortality due to respiratory diseases in children in São Paulo, Brazil: a preliminary report. *Environmental Research*. 1994;65(2):8.

.٤٩ Tunnicliffe W, Burge P, Ayres J. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *The Lancet*. 1994;344(8939):4.

.٥٠ Nemery B, Hoet PHM, Nemmar A. The Meuse Valley fog of 1930: an air pollution disaster. *The Lancet*. 2001;357(9257):704-8.

.٥١ Forsberg B, Stjernberg N, Linne R, Segerstedt B, Wall S. Daily air pollution levels and acute asthma in southern Sweden. *European respiratory journal*. 1998;12(4):6.

.٥٢ Castellsague J, Sunyer J, Saez M, Anto J. Short-term association between air pollution and emergency room visits for asthma in Barcelona. *Thorax*. 1995;50(10):6.

.٥٣ Segala C, Fauroux B, Just J, Pascual L, Grimfeld A, Neukirch F. Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. *European Respiratory Journal*. ١٩٩٨;١١(٣):٩.

.٥٤ Atkinson R, Anderson H, Strachan D, Bland J, Bremmer S, Ponce de Leon A. Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. *European Respiratory Journal*. 1999;13(2):8.

.٥٥ Hasselblad V, Eddy DM, Kotchmar DJ. Synthesis of environmental evidence: nitrogen dioxide epidemiology studies. *Journal of the Air & Waste Management Association*. ١٩٩٢;٤٢(٥):٩.

.٥٦ Brunekreef B, Holgate ST. Air pollution and health. *The Lancet*. 2002;360(9341):1233-42.

.٥٧ Nur Sinem Ozcan KMC. Evaluation of Air Pollution Effects on Asthma Disease: The case of

Izmir. *Procedia - Social and Behavioral Sciences* 2015;202:8.