

## EXPOSURE TO AIR POLLUTION AND RESPIRATORY DISORDERS: AN OVERVIEW

\*B. R. Pandey<sup>1,2</sup>, Gurpreet Kaur<sup>3</sup>

<sup>1</sup>Faculty of Science & Technology, Sai Nath University, Ranchi, Jharkhand, India, <sup>2</sup>Sky Institute, Lucknow, Uttar Pradesh, India, <sup>3</sup>Research Scholar, Sai Nath University, Ranchi, Jharkhand, India

\*Address for Correspondence: Dr. B. R. Pandey, Dean, Faculty of Science & Technology, Sai Nath University, Ranchi, Jharkhand, India & Director (Research), Sky Institute, Lucknow, Uttar Pradesh, India  
Email ID : drbrpandey@gmail.com

### ABSTRACT

*Air pollution continues to pose a significant threat to health worldwide. According to a WHO assessment of the burden of disease due to air pollution, more than two million premature deaths each year can be attributed to the effects of urban outdoor air pollution and indoor air pollution (from the burning of solid fuels). More than half of this disease burden is borne by the populations of developing countries. Scientific studies conducted during last sixty years have provided sufficient evidence to establish a correlation between exposure to air pollutants and the developing of severe respiratory disorders. When we breathe in dirty air, we bring air pollutants deep into our lungs, thus air pollution causes serious damage to the respiratory tract. Air pollution exposure can trigger new cases of asthma, exacerbate (worsen) a previously existing respiratory illness, and provoke development or progression of chronic illnesses including lung cancer, chronic bronchitis, chronic obstructive pulmonary disease, and emphysema. Air pollution is a complex mix of gases and particles. It has been seen that five pollutants generally account for 98 percent of air pollution which are carbon monoxide (CO), sulfur oxides, hydrocarbons, particulate matter, nitrogen oxides. Air pollutants enter the body predominantly through the lungs. Some of these chemicals are absorbed into the blood and some that are not absorbed are eliminated by the lungs and some are retained. Gaseous pollutants disseminate deeply into the alveoli, allowing its diffusion through the blood-air barrier to several organs. The site of deposition of aerosols in the respiratory tract depends on the size of the particle. Many particles are irregular in shape. There are a number of ways to delineate particle size or behavior like aerodynamic diameter, mass mean etc. Particulate matter (PM) is a mix of solid or liquid particles suspended in the air. Particulate matter is deposited at different levels of the respiratory tract, depending on its size: coarse particles (PM<sub>10</sub>) in upper airways and fine particles (PM<sub>2.5</sub>) can be accumulated in the lung parenchyma, inducing several respiratory diseases. Air pollution is a major environment-related health threat to children and a risk factor for both acute and chronic respiratory disease. Children with underlying chronic lung diseases, particularly asthma and cystic fibrosis, are especially vulnerable. Research studies have established that particulate matter may also produce different modifications during its passage through the airways, like inflammatory cells recruitment, with the release of cytokines and reactive oxygen species (ROS) which are capable to activate different pathways, such as MAP kinases, NF-κB, and Stat-1, or induce DNA adducts. These alterations can mediate obstructive or restrictive respiratory diseases like asthma, COPD, pulmonary fibrosis and even cancer. Mechanism of interaction of air pollutants with lung functions has not been fully understood. It has been argued that our ambient plays an important role in the composition and size of the particles, which are responsible for producing specific damage along the airways. Exposure to air pollution can increase inflammatory factors and cellular recruitment in the lung, which promotes physiology alterations resulting in complex pulmonary diseases like chronic obstructive pulmonary disease (COPD) and asthma. Particulate matter can activate other cellular mediators that produce pulmonary fibrosis. Acute exposure to particulate matter can activate Th2 immune responses and chronic exposure may change this profile by activation of Th1, and it triggers pro-fibrotic cytokines as well.*

*Air pollution threatens the health of entire populations. Air pollution is a growing global problem. Yet measures to controlling air pollution appear to be inadequate. The overall evidence from the past and present epidemiological research studies supports tighter standards for air pollution, especially particulate pollutants for sustainable public health in developed and developing countries. Air pollution is a modifiable risk factor and understanding the harmful effects on respiratory functions linked to it would enable preventive health measures to be taken in order to reduce air pollution levels and associated diseases and would be of further use to healthcare providers, regulatory agencies and researchers. In addition, a better understanding of the biological mechanisms linking indoor/outdoor air pollution and respiratory diseases might become a vital target in developing novel pharmacological strategies focused on decreasing adverse effects of air pollution on respiratory system. Moreover, the potential of organic medicinal herbs in prevention and treatment of air pollution mediated respiratory disorders such as bronchial asthma, chronic obstructive pulmonary disease, lung cancer, pulmonary fibrosis could not be ignored. The potential of organic medicinal herbs like Inula racemosa (Pushkarmool), Ocimum sanctum (Krishna Tulasi), Terminalia belerica (Vibhitaki), Piper longum (Pipali) in combination could be explored for these disease conditions. The organic polyherbal combination consisting of these medicinal herbs has shown beneficial response to asthmatic patients attending the clinic of International Institute of Herbal Medicine (IIHM), Lucknow, India, an R & D Wing of Organic India Limited, Lucknow, India. This polyherbal combination may be useful in respiratory allergies and all kinds of bronchial asthma, upper respiratory tract and lung infections. It can serve as an expectorant in dry cough and it has ability to improve lung capacity. In a case study of patient of lung cancer, the herbal treatment with polyherbal combination consisting of medicinal herbs namely Ashwagandha (Withania somnifera), Immunity: combination of Vana Tulsi (Ocimum gratissimum), Krishna Tulsi (Ocimum sanctum), Katuki (Picrorrhiza kurroa) was used as main agent for treating the lung cancer, while Breath Free: combination of Pushkarmool (Inula racemosa), Krishna Tulsi (Ocimum sanctum), Vibhatki (Terminalia belerica), Pippali (Piper longum) was used for symptomatic relief. These were continued for a period of two years. The treatment with combination of the above medicinal herbs produced not only beneficial effects but cured the patient after a period of two years as judged by marked improvement of his clinical condition and repeat radiological profile. Traditional systems of medicines are still in place today because of their organizational strengths and as they focus primarily on multi-component mixtures. They contain enormous number of biological compounds to fight the disease at various aspects. These herbal medicinal preparations may exert synergistic effects due to multi-constituents and multi-targets and these formulations can explore a wider biological space with less expense. These formulations may have capability to modulate the biological networks modestly and thus may be efficient in controlling complex disease systems. They have ability to produce effects at lower concentration of individual constituents, thus is safer than single component drugs. These herbal preparations can deal with drug resistance that becomes more and more severe with antibiotics, antimalarial and anticancer drugs. Thus, it would be desirable to conduct multidisciplinary research on herbal/traditional drugs in order to combat air pollution mediated respiratory disorders and other disease conditions for ailing humanity.*

**Keywords:** Air Pollution; Respiratory Diseases ; Pulmonary Function; Asthma ; Chronic Obstructive Pulmonary Disease; Chronic Bronchitis ; Lung Cancer; Pulmonary Fibrosis, Children Pulmonary Health; Organic Medicinal Herbs in Respiratory Disorders / Lung Cancer

## INTRODUCTION

In the present scenario of population explosion, industrialization, rapidly growing activities related to construction of roads and buildings, unexpected increase in vehicles for transportation and uses for individuals, changing lifestyles, air

pollution has become a serious problem all over the world and has emerged as a big threat to public health. Air pollution comes from transport, coal and other industrial power plants, industry, ships and from agricultural production, but also

from natural sources such as wildfires and volcanic eruptions. Pollutants in the air are often invisible, but they can have serious effects on our health. Climate change also has an effect: Warmer summers mean longer pollen seasons and heat waves create peak levels of pollution. In addition, it appears that the allergic potential of pollen increases when linked to air pollutants. As industrialization has taken on a global dimension since the end of World War II, so has pollution. Urban air pollution comprises a large number of toxic substances such as sulphur dioxide, ozone, nitrogen oxide, nitrogen dioxide, carbon monoxide, carbon dioxide, particulate matter, rubber dust, polycyclic aromatic hydrocarbons, Chloroflouro-carbons (CFCs), heavy metals and many different volatile organic compounds.

Atmospheric pollution released from readily identifiable sources is referred to as primary pollution while pollutants that occur as a result of a chemical reaction with or in the atmosphere are secondary pollutants. The categories of primary pollution sources are mobile or stationary, combustion or non-combustion, area or point sources, direct or indirect. Mobile sources include automobiles, trains, and airplanes. A point source is a stationary source whose emissions have significant impact on air quality while an area source is one which is not a significant polluter by itself but contributes to air pollution as part of a group of relatively small polluters. Not all forms of air pollution can be accounted for by "traditional" gaseous and particulate matter. Non-traditional forms of air pollution include noise, odor, heat, ionizing radiation, and electromagnetic fields. Although internal combustion engines (particularly two stroke and diesel engines which are prevalent in the developing world and in former East Bloc countries) are the most publicly visible sources of pollution, large quantities of pollutants are by-products of fossil-fuel burning industries - particularly coal fired power plants and metal smelters.

As we know particles are a heterogeneous mixture of solid and liquid droplets with wide distributions of size and mass. Coarse particles, greater than 2.5  $\mu\text{m}$  in median aerodynamic diameter, derive from a variety of sources including windblown dust and grinding operations; fine particles are primarily from the combustion of

fossil fuels.<sup>[1]</sup> Common constituents of particulates include elemental and organic carbon, sulphates, nitrates, pollen, microbial contaminants, and metals.<sup>[1]</sup> Fine particles can react with sulphur dioxide and oxides of nitrogen in the atmosphere to form strong acids, such as sulphuric acid, nitric acid, hydrochloric acid, and acid aerosols.<sup>[1]</sup> In addition, urban air also contains benzene and 1, 3-butadiene that are considered carcinogenic.<sup>[2]</sup> The health impact of outdoor air pollution became apparent during several historic episodes in London, England and in some other places.

The world's worst short-term civilian pollution crisis was the 1984 Bhopal Disaster in India.<sup>[3]</sup> Leaked industrial vapours from the Union Carbide factory, belonging to Union Carbide, Inc., U.S.A. (later bought by Dow Chemical Company), killed at least 3787 people and injured anywhere from 150,000 to 600,000. The United Kingdom suffered its worst air pollution event when the December 4 Great Smog of 1952 formed over London. In six days, more than 4,000 died and more recent estimates put the figure at nearer 12,000.<sup>[4]</sup> An accidental leak of anthrax spores from a biological warfare laboratory in the former USSR in 1979 near Sverdlovsk is believed to have caused at least 64 deaths.<sup>[5]</sup> The worst single incident of air pollution to occur in the US occurred in Donora, Pennsylvania in late October, 1948, when 20 people died and over 7,000 were injured.<sup>[6]</sup>

These episodes demonstrated conclusively that the confluence of adverse weather conditions and extremely high levels of pollution from ambient particles and sulphur dioxide can cause immediate and dramatic increases in mortality.<sup>[7,8]</sup>

Air pollution has been linked to many negative impacts on human health and on the health of the environment. In addition to the notorious episodes such as the London "black fog" of 1952 that killed thousands, pollution causes serious, ongoing general health hazards of a less conspicuous, but no less dangerous kind. Exposure to levels of air pollution that do not cause immediate acute illness or death are more difficult to assess. However, ambient air pollution has been implicated as a causal factor in (1) chronic respiratory and cardiovascular disease (2) alteration of body functions such as lung ventilation and oxygen transport (3) reduced work and athletic performance (4) sensory irritation of the eyes, nose,

and throat (5) aggravation of existing disease such as asthma. When we breathe in dirty air, air pollutants come into our lungs and cause serious damage to the respiratory tract. Air pollution exposure can trigger new cases of asthma, exacerbate (worsen) a previously existing respiratory illness, and provoke development or progression of chronic illnesses including lung cancer, chronic obstructive pulmonary disease, and emphysema. Air pollutants also negatively and significantly harm lung development, creating an additional risk factor for developing lung diseases later in life. Air pollution is a major environment-related health threat to children and a risk factor for both acute and chronic respiratory disease. While second-hand tobacco smoke and certain outdoor pollutants are known risk factors for respiratory infections, indoor air pollution from solid fuels is one of the major contributors to the global burden of disease. In poorly ventilated dwellings, indoor smoke can be 100 times higher than acceptable levels for small particles. Exposure is particularly high among women and young children, who spend the most time near the domestic hearth. Outdoor air pollution is large and increasing a consequence of the inefficient combustion of fuels for transport, power generation and other human activities like home heating and cooking. Combustion processes produce a complex mixture of pollutants that comprises of both primary emissions, such as diesel soot particles and lead, and the products of atmospheric transformation, such as ozone and sulfate particles.

Urban outdoor air pollution is estimated to cause 1.3 million deaths worldwide per year. Children are particularly at risk due to the immaturity of their respiratory organ systems. Those living in middle-income countries disproportionately experience this burden. Exposure to air pollutants is largely beyond the control of individuals and requires action by public authorities at the national, regional and even international levels. Indoor cooking and heating with biomass fuels (agricultural residues, dung, straw, wood) or coal produces high levels of indoor smoke that contains a variety of health-damaging pollutants. There is consistent evidence that exposure to indoor air pollution can lead to acute lower respiratory infections in children under age five, and chronic obstructive pulmonary disease and lung cancer in adults. Indoor air

pollution is responsible for 2 million deaths annually. Acute lower respiratory infections, in particular pneumonia, continue to be the biggest killer of young children and this toll almost exclusively falls on children in developing countries.

New stationary sources in homes are also sources of the newer photochemical pollutants such as the oxides of nitrogen from unflued gas cookers and heaters.<sup>[9]</sup> During the 1952 smog episode, there was a sharp rise in hospital admissions and visits to primary care physicians, but recent re-analysis<sup>[10]</sup> of the mortality data indicates the number of deaths was underestimated and was nearer 12,000. While the majority of deaths occurred in individuals with chronic respiratory disease, the steep rise in mortality was sustained for several months and did not drop immediately after the resolution of the smog episode. It seems that many of the exacerbations of preexisting respiratory illnesses occurred during the smog episodes were the result of acute respiratory infections (ARIs). Recent evidence from developing countries confirms the direct exposure-response relationship between indoor air pollution by combustion of biomass fuels generating high levels of particulates and sulphur dioxide with increased acute respiratory infections in adults and children.<sup>[11]</sup>

Studies have indicated that air pollution is a significant risk factor for a number of health conditions including respiratory infections, heart disease, chronic obstructive disease (COPD), stroke and lung cancer.<sup>[12]</sup> The health effects caused by air pollution may include difficulty in breathing, wheezing, coughing, asthma and worsening of existing respiratory and cardiac conditions. These effects can result in increased medication use, increased doctor or emergency room visits, more hospital admissions and premature death. The human health effects of poor air quality are far reaching, but principally affect the body's respiratory system and the cardiovascular system. Individual reactions to air pollutants depend on the type of pollutant a person is exposed to, the degree of exposure, and the individual's health status and genetics.<sup>[13]</sup> The most common sources of air pollution include particulates, ozone, nitrogen dioxide, and sulphur dioxide. Children aged less than five years that live in developing countries are the most vulnerable

population in terms of total deaths attributable to indoor and outdoor air pollution.<sup>[14]</sup> The present review focuses on respiratory disorders mediated through exposure to air pollution and underlying mechanisms of action which might be useful towards developing effective therapeutic strategy for the management of air pollution mediated respiratory diseases.

### EFFECTS ON RESPIRATORY FUNCTION

In the present era industrialization and fast changing life styles, we breathe in polluted air and experience various kinds of air pollution related symptoms such as watery eyes, coughing, or wheezing. Even for healthy people, polluted air can cause respiratory irritation or breathing difficulties during exercise or outdoor activities. The actual risk of individual is modulated by various factors such as health status, pollutant type and concentration, and the duration of exposure to the polluted air. Several epidemiological research studies have been conducted to investigate acute and chronic effects on health as a result of exposure to ambient air pollution and associations have been found between exposures occurring on the day of the event or the preceding days and daily non-accidental mortality, cardio-respiratory deaths, hospitalizations, and emergency room visits.<sup>[15-35]</sup>

The studies have shown that short-term elevations of ambient air pollution cause a variety of acute health events, especially in certain subgroups of the population, such as the elderly, children, and those with chronic ailments like congestive heart failure, diabetes, and cardiovascular disease.<sup>[32,36]</sup>

The studies have indicated that the following group of individuals is most susceptible to severe health problems from air pollution:

- Individuals with heart disease - such as coronary artery disease or congestive heart failure
- Individuals with lung disease - such as asthma, emphysema or chronic obstructive pulmonary disease (COPD)
- Pregnant women
- Outdoor worker
- Children under age 14, whose lungs are still developing
- Athletes who exercise vigorously outdoors

High air pollution levels can cause immediate health problems: (1) aggravated cardiovascular and

respiratory illness (2) added stress to heart and lungs, which must work harder to supply the body with oxygen (3) damaged cells in the respiratory system. Long-term exposure to polluted air can have permanent health effects: (1) accelerated aging of the lungs (2) loss of lung capacity (3) decreased lung function (4) development of diseases such as asthma, bronchitis, emphysema, and possibly cancer (4) shortened life span.

Research studies have shown that tobacco smoking and exposure to toxic chemicals are important risk factors in causation of lung cancer and respiratory disease.<sup>[37-45]</sup> In addition to these risk factors, research studies have also demonstrated that ambient air pollution is responsible for increasing the incidence and mortality from lung cancer and from cardio-pulmonary diseases,<sup>[46-49]</sup> being a threat for public health.

### Specific Pollutants affecting respiratory function

**Ground-level Ozone** : Ground-level ozone is formed when volatile organic compounds (VOCs) and oxides of nitrogen (NOx) react with the sun's ultraviolet rays. The primary source of VOCs and NOx is mobile sources, including cars, trucks, buses, construction equipment and agricultural equipment. Ground-level ozone reaches its highest level during the afternoon and early evening hours. High levels occur most often during the summer months. It is a strong irritant that can cause constriction of the airways, forcing the respiratory system to work harder in order to provide oxygen. It can also cause other health problems: (1) aggravated respiratory disease such as emphysema, bronchitis and asthma (2) damage to deep portions of the lungs, even after symptoms such as coughing or a sore throat disappear (3) wheezing, chest pain, dry throat, headache or nausea (4) reduced resistance to infection (5) increased fatigue (6) weakened athletic performance.

**Particulate Matter (PM):** Particulate Matter is a complex mixture that may contain soot, smoke, metals, nitrates, sulfates, dust, water and tire rubber. It can be directly emitted, as in smoke from a fire, or it can form in the atmosphere from reactions of gases such as nitrogen oxides. Suspended Particulate matter (SPM) refers to the mixture of solid and liquid particles in air. In a broader sense the term applies to matter in the

atmosphere classed into particles having a lower size limit of the order of  $10^{-3}$   $\mu\text{m}$  and an upper limit of 100  $\mu\text{m}$ . SPM, a complex mixture of organic and inorganic substances, is a ubiquitous air pollutant, arising from both natural and anthropogenic sources. Particulate matter (PM) that is 10  $\mu\text{m}$  or less in diameter is called as respirable suspended particulate matter (RSPM) or  $\text{PM}_{10}$ , it penetrates the respiratory system. RSPM is generally grouped into three modes: ultra fine (size range less than 0.1  $\mu\text{m}$ ), fine (0.7-1  $\mu\text{m}$ ) and coarse (1-10  $\mu\text{m}$ ).<sup>[50, 51]</sup> Respirable dust particle is the term for particles found in the air, including dust, dirt, soot, smoke and liquid droplets. Particles can be suspended in the air of long periods.<sup>[52]</sup> Most of cities in Northern India are afflicted with the presence of unusually high concentration of  $\text{PM}_{10}$  in the ambient environment posing a serious risk to human health.<sup>[53]</sup> The size of particles is directly linked to their potential for causing health problems. Small particles (known as  $\text{PM}_{2.5}$  or fine particulate matter) pose the greatest problems because they can get deep into our lungs and some may even get into our blood stream. Exposure to such particles can affect both our lungs and our heart. Scientific studies have linked long-term particle pollution, especially fine particles, with significant health problems including: (1) increased respiratory symptoms, such as irritation of the airways, coughing or difficulty breathing (2) decreased lung function (3) aggravated asthma (4) development of chronic respiratory disease in children (5) development of chronic bronchitis or chronic obstructive lung disease (6) irregular heartbeat (7) nonfatal heart attacks (8) premature death in people with heart or lung disease, including death from lung cancer. Short-term exposure to particles (hours or days) can: (1) aggravate lung disease causing asthma attacks and acute bronchitis (2) increase susceptibility to respiratory infections (4) cause heart attacks and arrhythmias in people with heart disease. Even healthy individuals may experience temporary symptoms, such as: (1) Irritation of the eyes, nose and throat (2) coughing (3) chest tightness (4) shortness of breath

Particulates cause carcinogenic effects, accumulate in lungs and interfere with ability of lungs to exchange gases. Prolonged exposure causes lung cancer and asthma. Cigarette smoking is responsible for greatest exposure to carbon

monoxide (CO). Exposure to air containing even 0.001% of CO for several hours can cause collapse, coma and even death. As CO remains attached to hemoglobin in the blood for a long time, it accumulates and reduces the oxygen carrying capacity of blood. This impairs thinking, causes headaches, drowsiness and nausea.  $\text{SO}_2$  irritates the respiratory tissues.  $\text{NO}_2$  can irritate lungs; aggravate asthma and susceptibility to influenza and common colds. Many volatile organic compounds (benzene and formaldehyde) and toxic particulates can cause mutations and cancer. Lead causes neurological problems and cancer.

The research studies have shown that on inhalation of carbon monoxide it combines selectively with hemoglobin of the blood (Hb) and form carboxyhemoglobin (CO Hb), resulting reduction in oxygen carrying capacity of blood. High carbon monoxide level is potentially deadly and fatal to human life as carbon monoxide is a very dangerous asphyxiant. Carbon monoxide causes headache, fatigue, impaired judgment and dizziness, it also affects the functioning of heart and brain.<sup>[54]</sup> All atmospheric substance that are not gases but may be suspended droplets, solid particle or mixture of the two are generally referred to as particulates. Particulate matter causes respiratory problems like asthma, reduction in visibility and cancer. It also affects lungs and tissues.<sup>[55]</sup> Oxides of nitrogen cause respiratory problem, asthma, lung irritation and pneumonia. Higher concentration of oxides of sulphur causes bronchitis. It also causes acid rain, sulfurous smog and reduced atmosphere visibility. Combination of particulate matter with sulphur oxides is more harmful than either of them separately.<sup>[54]</sup> Ozone is produced in the upper atmosphere by solar reaction. Small concentration of this gas diffuses downward and become the major concern in air pollution. It causes irritation of eyes nose and throat, headache in man.

Air pollution is recognized as a major threat to human health. The United Nations Environment Programme has estimated that globally 1.1 billion people breathe unhealthy air.<sup>[56]</sup> Epidemiological studies have shown that concentrations of ambient air particles are associated with a wide range of effects on human health, especially on the cardio-respiratory system.<sup>[57,58]</sup> A growing body of evidence indicates that particulate pollution increases daily deaths and hospital admissions throughout the

world.<sup>[59,60]</sup> Recent studies have reported an association between particulate air pollution and daily mortality rates. Air pollution significantly increases both morbidity and mortality in the general population.<sup>[61,62]</sup> High respiratory vulnerability has been widely acknowledged as a major component of the adverse health effects of air pollution.<sup>[63]</sup> However, during the last 15 years air pollution-induced cardiovascular toxicity has become the focus of intensive studies among cardiologists and specialists in environmental medicine.<sup>[64,65,66]</sup> Outdoor PM is estimated to be responsible for about 3% of adult cardiopulmonary disease mortality, about 5% of trachea, bronchus and lung cancer mortality, and about 1% of mortality in children from acute respiratory infection in urban areas worldwide. This amounts to about 0.80 million (1.2%) premature deaths and 6.4 million (0.5%) lost life years.<sup>[67]</sup> The World Health Organization (WHO) has estimated that urban air pollution is responsible for approximately 8,00,000 deaths and 4.6 million lost life-years each year around the globe. In a recent review studies relating to the monitoring of ambient air pollution in India and comparing the same with Indian National Ambient Air Quality Standards-2009 (Indian NAAQS-2009), it has been shown that Sulphur Dioxide(SO<sub>2</sub>), Nitrogen Dioxide(NO<sub>2</sub>), Particulate Matter (PM<sub>2.5</sub>, PM<sub>10</sub>), Ozone(O<sub>3</sub>), Lead (Pb), Carbon Monoxide (CO), Benzene (C<sub>6</sub>H<sub>6</sub>) and Nickel (Ni) are some of the parameters which have significant impact on environmental pollution.<sup>[68]</sup>

Air pollution exposure can trigger new cases of asthma, exacerbate (worsen) a previously existing respiratory illness, and provoke development or progression of chronic illnesses including lung cancer, chronic obstructive pulmonary disease, and emphysema. Air pollutants also negatively and significantly harm lung development, creating an additional risk factor for developing lung diseases later in life. Research studies have shown the link between outdoor air pollution and lung disease: chronic bronchitis, chronic obstructive pulmonary disease (COPD) and adult asthma. The results of EU-wide ESCAPE project have revealed that the ability of human lungs to function well is affected by exposure to air pollution. The number of new cases of reduced lung function and COPD is

directly related to how close people live to busy roads and to levels of chemical compounds known as nitrogen oxide (NO<sub>x</sub>) and nitrogen dioxide (NO<sub>2</sub>) in the air. Although the results were less clear on chronic bronchitis and asthma, this does not imply that poor air quality does not have an impact on these conditions. The research showed the inhalable particles in the air (PM<sub>10</sub>) to be of greatest concern. A significant association was established between exposure to higher levels of PM<sub>10</sub> in the air and the number of people developing chronic obstructive pulmonary disease (COPD).

Although smoking is a major cause of COPD and other lung disease, being exposed to dirty air can result in a range of consequences that can exacerbate the problem. The immediate effects range from irritations of the nose, eyes or throat to a need for patients to increase their medication, a visit to their doctor, hospitalization and premature mortality. The respiratory effects of air pollution depend on the type and mix of pollutants; the concentration in the air; the amount of time individuals are exposed to the pollutant; how much of the pollutant individuals breathe in; and how much of the pollutant penetrates individuals' lungs.

Depending on their size, particles can be deposited in the upper airways (nose and throat), the large conducting airways and/or the small peripheral airways and air sacs or alveoli. At all of these locations, particles may produce irritation and inflammation. Lung disease is increasingly common. COPD is predicted to become the third leading cause of death by 2030. According to the World Health Organization (WHO), COPD affects approximately 210 million people worldwide. In Europe, it affects between 4 and 10 percent of adults.

Research studies have shown that particulate matter (PM) is easily deposited on bifurcations or angle ramifications of the bronchial tree due to air flow and turbulence, increasing PM interaction with the mucous membrane through an impact process.<sup>[69]</sup> Once deposited on a particular region in the lung, particulate matter (PM) can penetrate/be absorbed by the mucous layer, generating local damage.<sup>[70]</sup> Several *in vitro* studies with DEP or carbon black have been done to evaluate the effects of particle accumulation in

macrophages and their phagocytic capacity.<sup>[71]</sup> Particulate matter (PM) has been found to produce damage to the whole respiratory apparatus. PM increases cellular permeability and reduces the mucociliary activity by production of reactive oxygen species (ROS) and cytokine releases. Particulate matter (PM) has been found as risk factor for pulmonary diseases such as chronic obstructive pulmonary disease (COPD), asthma, and fibrosis.<sup>[72]</sup>

### Asthma

Epidemiological studies have shown that air pollutants like dust, smoke, pollen and volatile organic compounds are key drivers for asthma attacks. In addition to these air pollutants, common outdoor pollutant triggers include ozone, carbon monoxide, sulfur dioxide and nitrogen oxides. Asthma, a chronic disease of the lungs characterized by inflammation and narrowing of the airways, causes a sensation of tightness in the chest, shortness of breath, wheezing, and coughing. If untreated, asthma episodes can be near fatal or even fatal. Asthma is not currently curable, and damage that is done to lung tissue during asthma attacks may lead to permanent damage. Ozone, one of the most widespread air pollutants in the US, is formed when volatile organic compounds react with nitrogen oxides in the presence of sunlight. Ozone irritates the lungs at concentrations which are fairly common in urban settings, particularly in summer months. Increases in ozone are linked to asthma and other lung diseases. For those with severe asthma, symptoms increase even when ambient ozone levels fall under the thresholds set by the EPA. Elevated ozone levels also aggravate pre-existing heart problems, like angina. Asthma has emerged as major health problem around the world. Research studies have confirmed that asthma is characterized by airway hyper responsiveness<sup>[73]</sup> obstruction<sup>[74]</sup> and chronic inflammation<sup>[75]</sup> in this condition, the reversibility of airway obstruction, either spontaneously or following treatment<sup>[76]</sup> is another issue to be considered seriously. It has been shown that in the asthmatic patients pulmonary cells respond to an allergen and produce Th2 response including interleukins such as IL-4 and IL-13. Other interleukins IL-3, IL-5, IL-17, IL-17A have also been found to play vital

role in producing Th2 response in asthmatic patients.<sup>[77,78,79]</sup> Acute exposures to particulate matter (PM) can activate the Th2 response, inhibiting INF- $\gamma$  production<sup>[80]</sup> and promoting an asthmatic condition. Research studies have shown that chronic exposure to PM may enhance Th1 response by activation of IL-12<sup>[81]</sup> and in turn trigger to INF- $\gamma$ .<sup>[82]</sup> Studies conducted in murine *Schistosomiasis Mansonii* model have revealed that Th1 response strongly suppresses the Th2 response.<sup>[81]</sup> Research studies conducted on asthma animal model have shown that that exposure to particulate matter (PM) increases the asthmatic process which reflects the adjuvant potential of PM in the generation of *de novo* asthma in mice.<sup>[79]</sup> Other studies have also revealed that exposures to PM may produce oxidative stress by increasing ROS production, interleukins (IL-1, IL-8), and maturation of B lymphocytes.<sup>[83,84]</sup> The studies have further indicated that exposure to particulate matter (PM) may activate Th2 response in the lung and leads to the production of inflammatory mediators like IgE or IgG.<sup>[85]</sup>

### Chronic Obstructive Pulmonary Disease (COPD), chronic bronchitis and emphysema

Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, is a chronic lung disease that makes it hard to breathe. COPD is a chronic progressive disease characterized by narrowing of the airways, but these changes are permanent rather than reversible. COPD is caused by exposure to pollutants that produce inflammation, an immunological response. In larger airways, the inflammatory response is referred to as chronic bronchitis. In the tiny air cells at the end of the lung's smallest passageways, it leads to destruction of tissue, or emphysema.<sup>[86,87]</sup> Although current and ex-smokers account for most patients with COPD, exposure to air pollutants plays an important role in the development of COPD and the origin and development of acute exacerbations. The research studies have shown that bacteria, viruses<sup>[87]</sup>, cigarette smoking<sup>[88]</sup> and exposure to indoor and outdoor air pollution<sup>[89]</sup> are main factors in exacerbation of chronic obstructive pulmonary disease COPD. It is characterized by chronic inflammation of the airways and lung

parenchyma, especially of neutrophils, activated macrophages, and lymphocytes.<sup>[90]</sup> The results of the clinical studies on COPD cases have revealed the increased levels of IL-6, TNF- $\alpha$ , and IL-1 $\beta$ . The patients of COPD have been observed to be more susceptible to urban particles<sup>[91]</sup> and strong association has been found with exposures to particulate matters (PM 2.5 and PM 10–2.5).<sup>[92]</sup> Increased levels of proinflammatory mediators IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and IL-8 produced by macrophages or epithelial cells have been observed in COPD patients.<sup>[93]</sup> Research studies have also indicated that exposure to PM<sub>10</sub> may produce NF- $\kappa$ B activation in COPD patients.<sup>[94,95]</sup>

### Lung Cancer

Mortality from lung cancer has been identified as a major cause of cancer deaths worldwide as the total number of cases and resulting deaths is increasing globally. Lung cancer occurs due to uncontrolled growth of malignant cells in one or both lungs and tracheo-bronchial tree. Most common symptoms of lung cancer are shortness of breath, coughing (including coughing up blood), and weight loss.<sup>[96]</sup> At present, there is no specific treatment for the cure of patient suffering from lung cancer. Although tobacco smoking is a causal factor for increasing incidents lung cancer, there are other risk factors including air pollution for developing lung cancer. Particulate matter and ozone in particular may affect mortality due to lung cancer. Research studies have shown that outdoor air pollution is responsible for lung cancer deaths and it has been identified as a major carcinogen. Particulate matters like PAHs and metals present in atmosphere produce oxidative stress and are strong mutagenic and carcino-genesis agents.<sup>[97,98,99]</sup> It has been found that cancers of the trachea, bronchus, or lung represented approximately 7% of total mortality attributable to PM<sub>2.5</sub> in 2010.<sup>[100]</sup> Studies have revealed that exposure to particulate matter (PM) may be responsible in developing lung cancer in non-smokers<sup>[101]</sup> however, the risk of developing lung cancer is higher in smokers.<sup>[102]</sup>

### Pulmonary Fibrosis

Pulmonary fibrosis (PF) is one of a family of related diseases called interstitial lung diseases that can result in lung scarring. As the lung tissue becomes scarred, it interferes with a person's ability to

breathe. Pulmonary fibrosis can develop slowly or quickly. In some people, the disease stays the same for years. Usually, a person's breathing symptoms become worse over time. A person with pulmonary fibrosis eventually may be short of breath even at rest. The symptoms of Pulmonary Fibrosis include (a) shortness of breath, particularly during exercise (b) dry, hacking cough (c) fast, shallow breathing (d) gradual unintended weight loss (e) tiredness (f) aching joints and muscles (g) clubbing (widening and rounding) of the tips of the fingers or toes. Clinical studies have shown that in most cases, there is no known cause for the disease. In these cases, it is called idiopathic pulmonary fibrosis or IPF. There are few environmental factors that may increase the risk of pulmonary fibrosis. These include (1) cigarette smoking (2) certain viral infections (3) exposure to environmental pollutants, including silica and hard metal dusts, bacteria and animal proteins, and gases and fumes (4) the use of certain medicines (5) genetics: some families have at least two members who have pulmonary fibrosis (6) Gastroesophageal reflux disease (GERD), a condition in which acid from the stomach backs up into the throat. Some people who have GERD may breathe in tiny drops of acid from their stomachs, which may injure the lungs. Research studies have demonstrated that exposure to ambient particles is responsible to cause pulmonary fibrosis<sup>[103]</sup>, a restrictive disease presenting an irreversible decrement of the vital capacity<sup>[104]</sup> followed by implication of cells as fibroblast, myofibroblast<sup>[105]</sup> and macrophage<sup>[106]</sup> producing an excess of extracellular matrix components<sup>[107]</sup> and an irreversible distortion of the lung's architecture.<sup>[108]</sup> In this complex disease scenario, transforming-growth-factor TGF- $\beta$ ,<sup>[109]</sup> a potent mediator of fibrogenesis<sup>[110]</sup> has been found to be responsible in stimulating the deposit of collagen fibers. As we know, the action of transforming-growth-factor (TGF)- $\beta$  following inflammatory responses is characterized by increased production of extracellular matrix (ECM) components, as well as mesenchymal cell proliferation, migration, and accumulation. Thus, TGF- $\beta$  is important for the induction of fibrosis often associated with chronic phases of inflammatory diseases. This common feature of TGF-related pathologies is observed in many

different organs. Additionally, interleukins IL-4 and IL-13 are also produced in this disease condition.<sup>[111]</sup>

It has been observed that ambient particles such as Al, Si, carbon black, TiO<sub>2</sub>, silicon oxide, talcum powder, asbestos and other fibers cause epithelial damage followed by producing an increase in levels of interleukins like IL-2<sup>[112]</sup> and IL-8.<sup>[113]</sup>

Research studies have shown that PM<sub>10</sub> may induce increases in the platelet-derived growth factor (PDGF), one of the numerous growth factors, or proteins regulating cell growth and division and a potent mitogen and chemotactic factor for interstitial cells<sup>[114]</sup> and NF-κB which is a protein complex controlling transcription of DNA, cytokine production and cell survival., are indispensable in survival factors that inhibits apoptosis and promotes proliferation<sup>[115]</sup>; it also provokes myofibroblast differentiation<sup>[113]</sup> and production of collagen fibers in the lung.<sup>[114]</sup>

Further, it has been found that proteases activity also increases in airway epithelial A549 cells exposed to PM<sub>10</sub>.<sup>[116]</sup> Research data have established an increase in protease activity, especially of MMP-2 and MMP-9 and a decrease in E-cadherin and β-catenin expression.<sup>[117]</sup> Other studies have also established occurrence of pulmonary fibrosis due to exposure of particulate matter (PM) like TiO<sub>2</sub>, carbon black nanoparticles and PM generate reactive oxygen species (ROS), which produces a proinflammatory activity and cytotoxic effects.<sup>[118,103, 119, 120, 121]</sup> These studies have indicated that the exposures to particles worsen damage in patients with pulmonary fibrosis.

### Children's Pulmonary Health

Children are particularly susceptible to the effects of air pollution. They breathe through their mouths, bypassing the filtering effects of the nasal passages and allowing pollutants to travel deeper into the lungs. They have a large lung surface area relative to their weight and inhale relatively more air, compared to adults. They also spend more time out of doors, particularly in the afternoons and during the summer months when ozone and other pollutant levels are at their highest. Further, children may ignore early symptoms of air pollution effects, such as an asthma exacerbation, leading to attacks of increased severity. Combine those factors with the adverse impact of some pollutants on lung

development and the immaturity of children's enzyme and immune systems that detoxify pollutants, and there are a series of factors that contribute to children's increased sensitivity to air pollutants. Several studies have been done to investigate the effects of air pollution on children respiratory health and it has been observed that there are increases in persistent cough and phlegm, bronchitis, and early respiratory infections in communities with poor air quality. Several scientific studies have shown associations between selected air pollutants and adverse health effects in children<sup>[122]</sup> which include childhood hospital admissions<sup>[123-127]</sup>, school absences<sup>[128]</sup>, physician visits for upper and lower respiratory illness<sup>[129]</sup>, deficits in lung function growth rates<sup>[130]</sup>, bronchitis and chronic cough<sup>[131, 132]</sup>, and increased infant mortality<sup>[133, 134, 135]</sup>. A recent review in Europe strongly recommended a reduction in children's exposure to air pollution.<sup>[136]</sup>

In a recent study to compare the pulmonary function of children living in urban area of Tirana city with children living in suburban area of the city, it has been observed after comparing the results of values of pulmonary function of two groups of children that differences were significant ( $p$  0.001), whereas comparing symptoms were for cough ( $p$  0.011) and for phlegm ( $p$  0.032). The results of the study have revealed that air pollution is associated with respiratory health of children causing a slight decrease in values of pulmonary function in children of urban area compared with those of suburban area.<sup>[137]</sup> Several epidemiological studies have revealed that outdoor air pollution adversely affects children's lung function which may increase their susceptibility to respiratory and cardiovascular disease in adulthood.<sup>[138-141]</sup> The results of studies have shown that exposure to air pollutants in infancy may alter lung development, with potential long-term consequences.<sup>[142]</sup> Further, a new study in *EHP* encompassing exposures at birth and at school age found that decreases in lung function were associated only with recent exposure.<sup>[146]</sup>

The results of cohort studies conducted in Sweden, northern and southern Germany, the United Kingdom and the Netherlands have revealed small but significant associations between decreased lung function and higher estimated levels of pollution at the children's home address at age 6–8,

but not at their address as a newborn. This finding suggests that the recent exposures were the more critical to current lung function.<sup>[144]</sup> Other studies have also indicated that exposure at more than one time point,<sup>[145,146]</sup> an association between later lung function and early-life exposure might have been expected and effects of air pollution on children's lung function may be reversible.<sup>[147, 148]</sup> Studies have also been conducted to see the effect of air pollution on lung development from 10 to 18 years and it has been suggested that deficits in lung function in adolescence set the stage for reduced lung function in adulthood.<sup>[149]</sup>

Further, a lower lung function in childhood may predispose children for asthma and chronic obstructive pulmonary disease later in life.

A study has been conducted to estimate the impact of outdoor air pollution on respiratory morbidity in children after controlling for the confounding effects of weather, season and other pollutants using data on respiratory hospital admissions in children (three age groups: < 1, 1–4, and 5–14 years) for five cities in Australia and two in New Zealand where significant increases across the cities were observed for hospital admissions in children for pneumonia and acute bronchitis (0,1–4 years), respiratory disease (0,1–4,5–14 years), and asthma (5–14 years). These increases were found for particulate matter with a diameter less than 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) and less than 10  $\mu\text{m}$  ( $\text{PM}_{10}$ ), nephelometry,  $\text{NO}_2$  and  $\text{SO}_2$ . The largest association found was a 6.0% increase in asthma admissions (5–14 years) in relation to a 5.1-ppb increase in 24-hour  $\text{NO}_2$ . A strong and consistent associations have been found between outdoor air pollution and short-term increases in childhood hospital admissions and these were distinct from any temperature (warm or cool) effects.<sup>[150]</sup> Other studies have also found associations between air pollutants and lung / respiratory infections in children.<sup>[151-191]</sup> In a recent study, a significant association between traffic-related pollution and the development of asthma exacerbations and respiratory infections in children born to atopic parents and in those suffering from recurrent wheezing or asthma has been found suggesting that environmental control may be crucial for respiratory health in children with underlying respiratory disease.<sup>[192]</sup>

## DISCUSSION

Air pollution is a serious worldwide problem due to its impact on human health. Air pollution has been linked to many negative impacts on human health. In addition to the notorious episodes such as the London "black fog" of 1952 that killed thousands, pollution causes serious ongoing general health hazards. Ambient air pollution has been implicated as a causal factor in (1) chronic respiratory and cardiovascular disease (2) alteration of body functions such as lung ventilation and oxygen transport (3) reduced work and athletic performance (4) sensory irritation of the eyes, nose, and throat (5) aggravation of existing disease such as asthma. Scientific studies conducted during last sixty years have provided sufficient evidence to establish a correlation between exposure to air pollutants and the developing of severe respiratory disorders. When we breathe in dirty air, we bring air pollutants deep into our lungs, thus air pollution causes serious damage to the respiratory tract. Air pollution exposure can trigger new cases of asthma, exacerbate (worsen) a previously existing respiratory illness, and provoke development or progression of chronic illnesses including lung cancer, chronic bronchitis, chronic obstructive pulmonary disease, and emphysema. Air pollutants also negatively and significantly harm lung development, creating an additional risk factor for developing lung diseases later in life. Research studies have shown the link between outdoor air pollution and lung disease: chronic bronchitis, chronic obstructive pulmonary disease (COPD) and adult asthma.

Air pollution is a complex mix of gases and particles. It has been seen that five pollutants generally account for 98 percent of air pollution which are carbon monoxide (CO), sulfur oxides, hydrocarbons, particulate matter, and nitrogen oxides. A distinction often is made between two kinds of pollution. The first is characterized by sulfur dioxide and smoke from incomplete combustion of coal and by conditions of fog and cool temperature. The second kind of pollution is characterized by hydrocarbons, oxides of nitrogen and photochemical oxidants. It is caused by automobile exhausts and occurs especially in areas where intense sunlight causes photochemical reactions in polluted air masses

that are trapped by a meteorological inversion layer. Transportation (particularly automobiles), industry, electric power generation, space heating, and refuse disposal are major sources of producing pollutants that are emitted in atmosphere. Air pollutants enter the body predominantly through the lungs. Some of these chemicals are absorbed into the blood and some that are not absorbed are eliminated by the lungs and some are retained. Gaseous pollutants disseminate deeply into the alveoli, allowing its diffusion through the blood–air barrier to several organs. The site of deposition of aerosols in the respiratory tract depends on the size of the particle. Many particles are irregular in shape. There are a number of ways to delineate particle size or behavior like aerodynamic diameter, mass mean etc. Particulate matter (PM) is a mix of solid or liquid particles suspended in the air. Particulate matter is deposited at different levels of the respiratory tract, depending on its size: coarse particles ( $PM_{10}$ ) in upper airways and fine particles ( $PM_{2.5}$ ) can be accumulated in the lung parenchyma, inducing several respiratory diseases. Further, particulate matter may contain organic, inorganic and biological compounds, which have potential to modify important physiological activities like alterations in cytokine production, coagulation factors balance, pulmonary function, respiratory symptoms and cardiac function. Research studies have established that particulate matter may also produce different modifications during its passage through the airways, like inflammatory cells recruitment, with the release of cytokines and reactive oxygen species (ROS) which are capable to activate different pathways, such as MAP kinases, NF- $\kappa$ B, and Stat-1, or induce DNA adducts. These alterations can mediate obstructive or restrictive respiratory diseases like asthma, COPD, pulmonary fibrosis and even cancer.

During the past decades of years, several studies have been conducted on the effects of controlled photochemical pollutant exposure ( $O_3$ ,  $NO_2$ ,  $SO_2$ ) alone and lung function effects in healthy individuals and those with pre-existing lung disease. These studies have found that Inhaled  $O_3$  provokes a dose-dependent fall in lung function and an increase in bronchial hyper-responsiveness to histamine. Little difference has been observed between subjects with asthma and healthy

individuals after  $O_3$  exposure. Inhalation of high concentrations of  $SO_2$  has been found to provoke acute airway bronchoconstriction in normal subjects whereas lower concentrations provoke the same response in asthmatic subjects. Inhalation of  $NO_2$  at higher concentrations has been found to induce no change in resting lung function in either normal or asthmatic subjects exposed to concentrations of  $1880\mu g/m^3$  or less. These studies have indicated that controlled exposure studies show largely modest effects on lung function and the pattern of response does not explain the epidemiological evidence, or the mechanisms of how these pollutants may interact with infectious agents. However, few studies suggest the role of oxidant pollutants in increasing susceptibility to respiratory virus infection.<sup>[193-197]</sup>

Research studies have shown that lung defense mechanisms against inhaled particles and gaseous pollutants include innate mechanisms such as aerodynamic filtration, mucociliary clearance, particle transport and detoxification by alveolar macrophages, as well as local and systemic innate and acquired antiviral immunity. In particular, alveolar macrophages provide an innate defense mechanism against bacteria and viruses. These functions can be modulated by exposure to  $NO_2$  and other pollutants in experimental models.<sup>[198-212]</sup>

There has been a series of studies alluding to the link between infection and air pollution particularly by nitrogen dioxide.<sup>[213]</sup>

Air pollution is a major environment-related health threat to children and a risk factor for both acute and chronic respiratory disease. While second-hand tobacco smoke and certain outdoor pollutants are known risk factors for respiratory infections, indoor air pollution from solid fuels is one of the major contributors to the global burden of disease. In poorly ventilated dwellings, indoor smoke can be 100 times higher than acceptable levels for small particles. Exposure is particularly high among women and young children, who spend the most time near the domestic hearth. As is evident from research studies, exposure to air pollutants in children could lead to adverse health impacts which include increases in mortality in very severe episodes; an increased risk of perinatal mortality in regions of higher pollution, and an increased general rate of mortality in children; increased acute respiratory disease morbidity;

aggravation of asthma, as shown by increased hospital emergency visits or admissions as well as in longitudinal panel studies; increased prevalence of respiratory symptoms in children, and infectious episodes of longer duration; lowered lung function in children when pollutants increase; lowered lung function in more polluted regions; increased sickness rates as indicated by kindergarten and school absences; the adverse effects of inhaled lead from automobile exhaust. It has been observed that these disease conditions become severe when high levels of outdoor pollution are combined with high levels of indoor pollution. Indoor cooking and heating with biomass fuels (agricultural residues, dung, straw, wood) or coal produces high levels of indoor smoke that contains a variety of health-damaging pollutants. There is consistent evidence that exposure to indoor air pollution can lead to acute lower respiratory infections in children under age five, and chronic obstructive pulmonary disease and lung cancer in adults. Indoor air pollution is responsible for 2 million deaths annually. Acute lower respiratory infections, in particular pneumonia, continue to be the biggest killer of young children and this toll almost exclusively falls on children in developing countries. Various periods of vulnerability characterize children. The intrauterine, perinatal and early childhood periods, during which the lungs are developing and maturing, are very vulnerable times. These are periods when the lungs are susceptible to injury by air pollutants. Exposure during these periods reduces the maximal functional capacity achieved in adult life and can lead to enhanced susceptibility during adulthood to infection and to the effects of such pollutants as tobacco smoke and those present in occupational exposures. Children with underlying chronic lung diseases, particularly asthma and cystic fibrosis, are especially vulnerable. These children are at greater risk of adverse effects from pollution than are healthy children. Also, children subject to higher exposures indoors – for example, from tobacco smoke or smoke from poorly maintained heating or cooking appliances – are at greater risk of being affected by outdoor pollutants.

Several physiological and biological reasons/factors have been suggested to explain the susceptibility of young children to air pollution's

effects. As we know, in case of children lungs, immune system and brain are immature at birth and continue to develop until approximately age 6, and the cell layer lining the inside of the respiratory tract is particularly permeable during this age period. Compared to adults, children also have a larger lung surface area in relation to their body weight, and breathe 50% more air per kilogram of body weight. The process of early growth and development is important for the health of the child in general, and therefore may also be a critical time when air pollution exposures can have lasting effects on future health. Additionally, children tend to spend more time outdoors doing strenuous activities, such as playing sports, so they are breathing more outdoor air compared to adults, who spend on average about 90% of their time indoors. Research studies have also established that air pollution causes adverse effects of air pollution on different pregnancy outcomes and infant health. Air pollution, with concentrations typical of many European cities, increases the risk of death from respiratory causes in the postneonatal period. Further, strong associations exist between exposure to ambient air pollutants and adverse effects on the development of lung function. Reversible lung function deficits, chronically reduced lung growth rates and lower lung function levels are associated with exposure to air pollution. Moreover, research studies have found relationships for particulate matter and traffic-related air pollution (indicated by nitrogen dioxide) than for other pollutants. Air pollutants seem to interact with other environmental factors, such as allergens, viruses and diet that influence the overall impact of air pollutants on children's health.

Mechanism of interaction of air pollutants with lung functions has not been fully understood. It has been argued that our ambient plays an important role in the composition and size of the particles, which are responsible for producing specific damage along the airways. Exposure to air pollution can increase inflammatory factors and cellular recruitment in the lung, which promotes physiology alterations resulting in complex pulmonary diseases like chronic obstructive pulmonary disease (COPD) and asthma. Particulate matter can activate other cellular mediators that produce pulmonary fibrosis. Acute

exposure to particulate matter can activate Th2 immune responses and chronic exposure may change this profile by activation of Th1, and it triggers pro-fibrotic cytokines as well.<sup>[214]</sup>

It has been well established that cytokines are the hormonal messengers responsible for most of the biological effects in the immune system, such as cell mediated immunity and allergic type responses. Although they are numerous, cytokines can be functionally divided into two groups: those that are proinflammatory and those that are essentially anti-inflammatory but that promote allergic responses. Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses. Interferon gamma is the main Th1 cytokine. Excessive proinflammatory responses can lead to uncontrolled tissue damage, so there needs to be a mechanism to counteract this. The Th2-type cytokines include interleukins 4, 5, and 13, which are associated with the promotion of IgE and eosinophilic responses in atopy, and interleukin-10, which has more of an anti-inflammatory response. In excess, Th2 responses will counteract the Th1 mediated microbicidal action. The optimal scenario would therefore seem to be that humans should produce a well balanced Th1 and Th2 response, suited to the immune challenge.<sup>[215]</sup> All components present in the particulate form a final complex mixture responsible to produce or activate inflammatory processes, damage or ROS in the lung. These changes harm the epithelium, increasing epithelial permeability. In patients with pulmonary diseases, the exposure to particulate matter increases the changes and the lung damage.

Thus, vast majority of serious morbidity and mortality related to air pollution occurs *via* interactions with respiratory infection. Improving air quality can reduce the burden of respiratory disease and could improve public health. Reduced exposure to air pollution seems to improve children's health. As of yet, however, relatively few studies have looked at the effects of reduced air pollution. Nevertheless, existing studies show that reduced exposure to air pollutants can lead to a decrease in hospital admissions for respiratory complaints, a lower prevalence of bronchitis and respiratory infections, and improvement in lung

function growth rates. Animal studies have shown that ultra fine particle can cause inflammation in respiratory systems and greater allergic reactions and diesel particles can carry allergens into the body, resulting in a magnified allergic sensitivity and response. These particles may have important effects on the lung, and the fact that children's lungs may be more susceptible to damage, additional research on the effects of ultra fine particles in the context of children's respiratory health are needed. While there is emerging evidence confirming that air pollutants are intimately related to infections, further research studies on interactions with co-factors like allergens, domestic biomass fuel combustion, and diet and virus infections would help in understanding the mechanism of producing adverse effects of air pollutants on lung function.

Air pollution threatens the health of entire populations. Air pollution is a growing global problem. Yet measures to controlling air pollution appear to be inadequate. The overall evidence from the past and present epidemiological research studies supports tighter standards for air pollution, especially particulate pollutants for sustainable public health in developed and developing countries. Air pollution is a modifiable risk factor and understanding the harmful effects on respiratory functions linked to it would enable preventive health measures to be taken in order to reduce air pollution levels and associated diseases and would be of further use to healthcare providers, regulatory agencies and researchers. In addition, a better understanding of the biological mechanisms linking indoor/outdoor air pollution and respiratory diseases might become a vital target in developing novel pharmacological strategies focused on decreasing adverse effects of air pollution on respiratory system. Moreover, the potential of organic medicinal herbs in prevention and treatment of air pollution mediated respiratory disorders such as bronchial asthma, chronic obstructive pulmonary disease, lung cancer, pulmonary fibrosis could not be ignored. The potential of organic medicinal herbs like *Inula racemosa* (Pushkarmool), *Ocimum sanctum* (Krishna Tulasi), *Terminalia belerica* (Vibhitaki), *Piper longum* (Pipali) in combination could be explored for these disease conditions. The organic

polyherbal combination consisting of these medicinal herbs has shown beneficial response to asthmatic patients attending the clinic of International Institute of Herbal Medicine (IIHM), Lucknow, India, an R &D Wing of Organic India Limited, Lucknow, India. This poly herbal combination may be useful in respiratory allergies and all kinds of bronchial asthma, upper respiratory tract and lung infections. It can serve as an expectorant in dry cough and it has ability to improve lung capacity. In a case study of patient with lung cancer, the herbal treatment with polyherbal combination consisting of medicinal herbs namely Ashwagandha (*Withania somnifera*), Immunity: combination of Vana Tulsi (*Ocimum gratissimum*), Krishna Tulsi (*Ocimum sanctum*), Katuki (*Picrorrhiza kurroa*) was used as main agent for treating the lung cancer, while Breath Free: combination of Pushkarmool (*Inula racemosa*), Krishna Tulsi (*Ocimum sanctum*), Vibhatki (*Terminalia bellerica*), Pippali (*Piper longum*) was used for symptomatic relief. These were continued for a period of two years. The treatment with combination of the above medicinal herbs produced not only beneficial effects but cured the patient after a period of two years as judged by marked improvement of his clinical condition and repeat radiological profile.<sup>[216]</sup>

Traditional systems of medicines are still in place today because of their organizational strengths and as they focus primarily on multi-component mixtures. They contain enormous number of biological compounds to fight the disease at various aspects. These herbal medicinal preparations may exert synergistic effects due to multi-constituents and multi-targets and these formulations can explore a wider biological space with less expense. These formulations may have capability to modulate the biological networks modestly and thus may be efficient in controlling complex disease systems. They have ability to produce effects at lower concentration of individual constituents, thus is safer than single component drugs. These herbal preparations can deal with drug resistance that becomes more and more severe with antibiotics, antimalarial and anticancer drugs. Thus, it would be desirable to conduct multidisciplinary research on herbal/traditional drugs in order to combat air pollution mediated respiratory disorders and other disease conditions for ailing humanity.

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