Chapter 7
Air Pollution Exposure Studies Related to Human Health

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Abstract Air is a complex amalgamation of gases, water vapor, and dust particles. With development in civilized human society and later on boom in industrialization, there is drastic change in the air quality levels. Levels of different gaseous pollutants, heavy metals, particulate matter, volatile organic compounds, and other pollutants are constantly rising up in the air majorly due to combustion of solid fuels and fossil fuels. All these pollutants greatly diverge in their chemical composition, reaction time and mechanism of action. Depending on the exposure time and concentration, these pollutants can exert various toxicological impacts on human health such as respiratory, neurological, and cardiovascular disorder and other life-threatening diseases like cancer. Air pollution has also been connected with premature child birth, morbidity, mortality and reduced life expectancy. In this chapter, the sources of air pollution their effects on different organs and systems in human body as well as their mechanism of action will be discussed.

Keywords Air pollution · Pollutants · Particulate matter · Heavy metals · Human health · Cardiovascular · Pulmonary · Digestive system · Nervous system · Skin · Cancer

7.1 Introduction

One of the major conundrums with which mankind is struggling today is air pollution. Air pollution is the heterogeneous concoction of the gases, water vapor, and particulate matter (PM) in the air. Nowadays, air quality is significantly getting deteriorated mainly because of rapid industrialization and urbanization that can impact the human health and environment. The impact of air quality on human health is at an alarming stage where nine out of ten people breathe polluted air which

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sums up to 7 million deaths (one out of eight deaths globally) in 2012 solely due to polluted air exposure (WHO 2014). Substances which are responsible for causing deleterious impacts on the environment are categorized as pollutants. Pollutants are mainly divided into two categories as primary pollutants, which mainly consists of particles or particulate matter (PM), sulfur oxides (SO_X), nitrogen oxides (NO_X), volatile organic compounds (VOCs), and oxides of carbon and secondary pollutants such as ground-level ozone (O_3) which are derived from primary air pollutants (Saxena and Sonwani 2019a, b; Türk and Kavraz 2011).

Every living being is exposed to the air pollution every day, some to a more and some to a less extent depending on their lifestyle and socioeconomic status (Rückerl et al. 2011). The effect of air quality impacts the human health directly as on an average a person inhales around 500 million liters of air (12,000–16,000 liters of air daily) (Saxena and Sonwani 2019a, b; Türk and Kavraz 2011). The first study about the effects of air pollution was performed in the Meuse Valley, Belgium, where more than 60 people died because of smog in 1930 (Firket 1936). Mechanistic, epidemiological, clinical, and experimental studies have provided numerous evidences supporting the adverse and detrimental effects of long-term and short-term exposure to air pollution on human health. The aim of this chapter concentrates on identifying different sources of air pollution, types of pollutants, and mainly their impact on overall human health and functioning of different organs and systems in human body independently and in combined manner.

7.2 Types of Air Pollution Impacting Human Health

Indoor Air Pollution (IAP)

Indoor air quality (IAQ) is a parameter that refers to the quality of air inside and the surrounding residential area, shopping complexes, schools and colleges, gym etc.

IAP is ubiquitous and of major concern globally. Both urban and rural societies are directly affected by the indoor air pollution but the source and the type of pollutant to which each society is exposed varies differently. The risk of getting affected by air pollution is more profound in underdeveloped or developing countries especially because of the smoke emitted from the combustion of solid fuels such as coal and biomass (wood, crop residue, animal dung, etc.) (Sonwani and Kulshreshtha 2016). Combustion of coal and other solid fuels can produce variant pollutants such as CO, NO_x, SO_x, PM, benzene, and polycyclic aromatic hydrocarbons (PAH) as well as various toxic element such as mercury, selenium, arsenic, lead, and fluorine (Sonwani et al. 2016; Kurt et al. 2016). Whereas, developed societies are mostly exposed to the semi-volatile and volatile organic compounds. Another source of IAP is Tobacco Smoking (TS). It has been known for centuries that TS is injurious for the health of the smoker but recently the health concern has been raised for those who do not smoke directly and instead inhale the smoke from the primary smoker, hence are known as passive or involuntary smokers, especially the children and infants. Tobacco smoke is usually similar to other types of smokes,

Table 7.1 Comparison of number of deaths caused by outdoor and indoor pollution (shown in percentage) WHO 2014

Diseases	Outdoor air pollution (in percentage)	Indoor air pollution (in percentage)
Ischemic heart disease	40	26
Stroke	40	34
Chronic obstructive pulmonary disease (COPD)	11	22
Lung cancer	6	6
Acute lower respiratory infection (in children)	3	12

a heterogeneous mixture of gases, tiny particles, and chemical carcinogens (Saxena and Ghosh 2012).

Recent literatures have established direct and strong correlation between the exposure of smoke from solid fuels and occurrence of various acute and chronic infections and diseases such as acute respiratory tract infections (ARI), chronic obstructive pulmonary disease (COPD), and lung cancer (Zhang and Smith 2003; Torres-Duque et al. 2008; Smith-Sivertsen et al. 2009; Perez-Padilla et al. 2010; Sood 2012; Chen and Modrek 2018).

Outdoor Air Pollution (OAP)

The sources of OAP are varied unlike the IAP, both natural and anthropogenic activities play crucial role in determining the quality of the air. Nevertheless, the pollutants present in outdoor air are mostly similar to indoor air but their concentrations are different and usually higher. Natural sources of air pollution include volcanic eruption, lightning, forest and brush fires, pollen grains, etc. Though natural sources has always been around us but in most of the cases it has never been any threat to mankind. Perhaps, pollution caused by anthropogenic activities is of major concern in today's time. Unstoppable urbanization and modernization of societies are highly responsible for worsening the air quality. Burning of fossil fuels and garbage, smoke emission from transport, power generation and industries are some of the major sources of outdoor air pollution.

Another study has raised an imperative concern about the transport of PM, ozone, and the toxic compounds over large distances, such as movement of dust particles from Mongolia to Western United States or the deposition of the dust from Saharan region to the Caribbean countries (Kurt et al. 2016).

Both indoor and outdoor air pollution are of equal concern and threat for human health as both affect the different sections of the society. Table 7.1 outlines the breakdown of the number of deaths because of various cardiopulmonary diseases caused by outdoor and indoor air pollution independently.

7.3 Pollutants Are Categorized into Four Major Categories Depending on Their Physical and Chemical Nature

1. Gaseous pollutants (e.g., SO_x, NO_x, CO_x, O_3, volatile organic compounds, such as Benzo(a)pyrene, BaP)
2. Persistent organic pollutants (POPs)
3. Heavy metals (e.g., lead, mercury, arsenic, chromium, etc.)
4. Respirable particulate matter ($PM_{2.5}$ and PM_{10})

7.3.1 Gaseous Pollutants (e.g., SO_2, NO_x, CO_x, O_3, Volatile Organic Compounds (VOCs), Such as Benzo(a)pyrene (BaP)

Gaseous pollutants are very common and most ubiquitous source of air pollution and are mainly produced by burning of fossil fuels in industries, vehicles, and homes resulting in the emission of many noxious gases such as carbon monoxide (CO), sulfur oxides (SO_x), nitrogen oxides (NO_x), volatile organic compounds (VOCs), and soot particles (Sonwani and Saxena 2016).

Out of all the pollutants, CO is considered as one of the major toxic pollutants present in the environment. Gases like SO_x and NO_x are toxic when inhaled in high concentrations, besides that they are involved in secondary particle formation when they react with ammonia (used mainly in agriculture) (Wang et al. 2015). Ground-level ozone is a secondary pollutant and is formed because of the photochemical reaction involving the interaction of nitrogen oxides and organic compounds in the presence of sunlight (Schultz et al. 2017).

VOCs are mostly released from the combustion process during the energy production and road transport. VOCs are mostly organic in nature such as benzene; when inhaled in large quantity they can cause hematological problems and cancer along with serious respiratory system damage (Kampa and Castanas 2008; Sonwani et al. 2016; Saxena and Ghosh 2015, 2019; Saxena 2015).

7.3.2 Persistent Organic Pollutants (POPs) (e.g., Dioxins)

POPs are composed of organic chemicals (polyhalogenated hydrocarbons that contain chlorine, bromine, or fluorine) that remain in the environment for a long period of time. POPs are lipophilic in nature and have certain other characteristics on the basis of which they are identified, such as their toxicity, bioaccumulation potential, persistence capabilities, and their ability for long distance transport (Beyer et al. 2000). They enter into the environment through pesticides and certain industrial chemicals and are ubiquitous; because of their long persistence potential

they tend to bioaccumulate and biomagnify, eventually entering into the food chain (WHO 2010). Their distribution is not regional or confined to a place; they are globally distributed through air, water, ocean currents, and polluted living organisms. Human can be exposed to POPs in a variety of ways including inhalation, oral ingestion, or direct contact with skin (Kim et al. 2013; Wang et al. 2012). Long-term exposure to POPs can cause serious concern to human health including cancer, neurodegenerative disease, birth defects, and sterility and immune defects. Children are more vulnerable to be affected by exposure to different pollutants compared to the adults (WHO 2010; Ruzzin 2012).

7.3.3 Heavy Metals

Heavy metals usually refer to the metals with relatively high atomic weight and density (more than 4 g/cm^3) which is usually 5 times greater than water and are generally toxic to human health even when present in low concentration, along with the density, chemical properties of metal are of equal concern. Some of the heavy metals commonly found in environment as contaminants are lead (Pb), copper (Cu), manganese (Mn), magnesium (Mg), cadmium (Cd), mercury (Hg), iron (Fe), zinc (Zn), chromium (Cr), cobalt (Co), arsenic (as), molybdenum (Mo), and selenium (Se) (Duruibe et al. 2007; Tchounwou et al. 2012). They are present in trace amounts in the environment and hence also known as trace elements (ppb range to less than 10 ppm) (Tchounwou et al. 2012).

Both natural and anthropogenic activities contribute to the high concentrations of heavy metals in the environment (Aksu 2015). With advancement in industries and the large-scale application of heavy metals in medical, technology, and defense lead to the wide distribution of heavy metals in the environment (Tchounwou et al. 2012). Exposure to heavy metals are known to affect cellular components (such as nucleic acid, proteins, and lipids) and its organelles such as nucleus, mitochondria, endoplasmic reticulum, lysosome, cell membrane, and enzymes involved in metabolism, detoxification, and damage repair (Squibb and Fowler 1981; Wang and Shi 2001). The toxicity caused by heavy metals such as arsenic, cadmium, chromium, and nickel can trigger DNA damage by base pair mutations and insertions–deletions or attack of reactive oxygen species on DNA (Landolph 1994). They can cause toxicity by inhalation, ingestion, and direct dermal contact (Tchounwou et al. 2012).

7.3.4 Respirable Particulate Matter ($PM_{2.5}$ and PM_{10})

Particulate matter (PM) is also known as particle pollution, and is one of the major forms of airborne pollutants found in both modern as well as underdeveloped countries. It is a complex amalgam of very tiny solid and liquid particles of varying chemistry and size present in the air around us (Brook 2007). PMs are very fine

particles which are classified on the basis of their aerodynamic diameter: coarse (diameter $<$ 10 μm; PM_{10}), fine (diameter $<$ 2.5 μm; $PM_{2.5}$), and ultrafine (nanoparticles diameter $<$ 0.1 μm; $PM_{0.1}$) (Mannuccio et al. 2015; Sonwani and Kulshrestha 2019).

Coarse particles are usually of high pH and basic in nature whereas smaller particles are often acidic in nature (Dockery and Pope 1994). Major sources for fine particles are vehicles, power plants, industrial and residential plants. It can have exacerbated effects on human health. These fine particles travel with air and get deposited into the respiratory tract. Different PM has different effect depending on its size and aerodynamic diameter (Lee et al. 2014; Sonwani and Kulshrestha 2018). PM_{10} particles usually originate from the dust from the road and agriculture, combustion of wood and solid fuels such as charcoal, demolition of buildings and mining activities (Block and Calderón-Garcidueñas 2009). $PM_{2.5}$ particles are very tiny and emerge from the gas or the condensation of the vapors during combustion of fossil fuels or industrial emission and are composed of both organic and inorganic compounds (Block and Calderón-Garcidueñas 2009). $PM_{2.5}$ is alone known to be responsible for nearly 3.3 million deaths per year globally and long-term exposure with $PM_{2.5}$ by10 μg/m^3 can increase the rate of cardiovascular mortality up to 11% (Kurt et al. 2016; Saxena and Sonwani 2019a, b).

The complexity of pollutants present in both outdoor and indoor air is mostly similar in composition; it only varies in the concentration of different pollutants in the air because of the different sources. Hence, Table 7.2 summarizes the source of all the major pollutants in outdoor and indoor air.

7.4 Impact of Air Pollution on Human Health

Numerous studies have established a correlation between air quality and human health. Deterioration in the quality of air is usually associated with increase in the cardiopulmonary mortality cases and exacerbation in the morbidity and mortality. Air pollution can affect our health directly in many ways depending upon various factors such as exposure time, intensity of pollution, type of pollutants exposed to, and general health status of the population. Different pollutants can affect our bodies in many different ways by altering the normal functioning of different body parts. Heart attacks, respiratory disease, and lung cancer rates are significantly higher in the population who breathe polluted air compared to those who live in comparatively cleaner environment (Mabahwi et al. 2014; Sonwani and Kulshrestha 2016). Figure 7.1 summarizes the effect of air pollution on different body systems and organs.

Table 7.2 Different pollutant sources contaminating outdoor and indoor air

Pollutants	Indoor air pollution source	Outdoor air pollution source
Fine particles ($PM_{2.5}$, PM_5, PM_{10})	Fuel or tobacco combustion, cleaning, cooking	Industries, agriculture, construction and demolition activities
Carbon monoxide	Fuel or tobacco combustion	Vehicle exhaust, industries, power plants
Polycyclic aromatic hydrocarbons	Fuel or tobacco combustion, cooking, residential heating.	Vehicles exhaust, petroleum product spillage, sewage sludge and tarry or creosote waste materials
Nitrogen oxides	Fuel combustion	Vehicle exhaust, power plants
Sulfur oxides	Coal combustion	Industries and automobiles
Arsenic and fluorine	Coal combustion	Agricultural chemicals, mining, metal smelting, burning of fossil fuels
Volatile and semi-volatile organic compounds	Fuel or tobacco combustion, consumer products, furnishing, construction materials, cooking	Automobile emission, gasoline marketing and storage tanks, petroleum and chemical industries, dry cleaning and natural gas combustion
Aldehydes	Fuel or tobacco combustion, consumer products, furnishing, construction materials, cooking	Industries, chemical production, power plants
Pesticides	Consumer products, dust from outside	Agricultural chemicals
Lead	Remodeling and demolition of painted surfaces	Vehicle combustion, industries, power plants
Biological pollutant	Moist areas, ventilation system, furnishings	Pollen grains, spores from fungi
Radon	Soil under building, construction materials	Construction materials
Free radicals and other short-lived, highly reactive compounds	Indoor chemistry	Vehicle exhaust, combustion of fossil fuel, power plants, industries

7.5 Respiratory System

Air pollution has direct effect on respiratory system. Increase in the number of cases and exacerbation in the diseases like chronic obstructive pulmonary disease (COPD), asthma, respiratory infection, and lung cancer has been observed with increase in the levels of pollutant in the air (Sunyer et al. 1997; Chen et al. 2014; Jiang et al. 2016). PM present in air enters into the respiratory system during breathing and tends to get deposited (Ni et al. 2015). Particles with size greater than 5 μm get deposited in the upper airways or lower larger airways, instead of smaller particles, less than 5 μm in size enters into the smaller areas of the respiratory system such as trachea, bronchioles, and alveoli (Dockery and Pope 1994). Although human body has devised several mechanisms to eliminate these particles when found in small quantities. Particles deposited in the trachea and alveoli are usually

Fig. 7.1 Air pollution affecting different body systems and organs

expelled by coughing whereas particles deposited beyond the terminal bronchioles are taken care by phagocytic cells such as macrophages (Dockery and Pope 1994). Gaseous pollutants have direct and immediate impact on the normal functioning of respiratory system. SO_2 can cause irritation in eyes, nose, and throat upon short-term exposure, where in long-term exposure of SO_2 can cause diseases including asthma, emphysema, bronchitis, and lung cancer (Kulle et al. 1986; Liu et al. 2016; Chen et al. 2014). Exposure of the pollutants such as PM, CO, SO_x, NO_x, and O_3 during the prenatal and postnatal developmental period results in decreased lung function, increasing the risk of developing respiratory infection and diseases later in the life (Wang and Pinkerton 2007; Mortimer et al. 2008).

7.5.1 Asthma and Respiratory Disorder

Air pollution is known to increase the incidence of asthma and can also exacerbate preexisting asthma. It is the most common chronic disease found among children and adolescents (Asher and Pearce 2014). Two major characteristic features known as the symptoms of asthma are: inflammation and hyperresponsiveness; in the airway and lungs they are usually triggered by alteration in the levels of different pollutants such as O_3, NO_2, and $PM_{2.5}$ (Aris et al. 1993; Frampton et al. 2002; Guarnieri and Balmes 2014). Excessive exposure to ozone can cause hole in lung tissues which can cause decrement in lung function, asthma, and other respiratory disorders, whereas inhalation of excess SO_2 is mainly responsible for causing more prominent bronchoconstriction (Seltzer et al. 1986; Johns and Linn 2011; Shrivastava et al. 2017). Samoli et al. (2011) studied the acute effect of PM_{10}, SO_2, NO_2, and O_3 exposure on the emergency admission of children due to exacerbation of asthma among age group of 0–14 years, from the year 2001 to 2004 where 10 μg/m^3 increase in the level of PM_{10} and SO_2 was associated with 2.5% increase (95% CI: 0.1–5.0) and 6% increase (95% CI: 0.9–11.3), respectively. From the year 1992 to 1998 the reduction in levels of pollution have reduced the asthma rate significantly upto14% and levels of CO significantly affected the rate of hospitalization because of asthma among children of 1–18 years of age groups (Neidell 2004). Another study conducted in Copenhagen, Denmark, examined the acute effect of different air pollutants affecting the children of age group 0–18 year by monitoring the increase in the number of emergency admission in hospital due to asthma. They found a significant association between hospital admission of children and different pollutants, NO_x (OR—1.11; 95% CI 1.05 to 1.17), NO_2 (OR—1.10; 95% CI 1.04 to 1.16), PM_{10} (OR—1.07; 95% CI 1.03 to 1.12), and $PM_{2.5}$ (OR—1.09; 95% CI 1.04 to 1.13) (Iskandar et al. 2012). Another study conducted in four major cities of Europe, during the year 1986–1992 found that there is significant increase in the hospital admission of adults with increase in the ambient levels of NO_2 (relative risk (RR) per 50 μg/m^3 increase 1.03, 95% CI 1.003 to 1.055) (Sunyer et al. 1997). In a controlled study where eight asthmatic patients were expose to 0.4 ppm of NO_2 for 1 hr. have shown the early bronchoconstrictor response (Belanger et al. 2006).

Heavy metals are known to exacerbate the existing asthma and kindle the inflammatory response in lungs and airway passage. Strong association has been found between the exposure of heavy metals and prevalence and exacerbation of asthma (Novey et al. 1983). Exposure to high levels of chromium (IV) can result in breathing problems and asthma (Das et al. 2011). Higher concentration of lead in blood (>5 μg/dL) is positively correlated with asthma (Zeng et al. 2016; Wu et al. 2019) whereas higher concentration of chromium and manganese in blood is related with more coughing and wheezing (Zeng et al. 2016). Exposure to the heavy metal fumes of zinc and mercury can cause temporary respiratory problems, bronchitis and asthma (Kawane et al. 1988; Jaishankar et al. 2014).

7.5.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD is responsible for 2% of total global diseases and is the third major cause of deaths among women in developing countries as they are exposed to the smoke emitted from the burning of the solid fuels while cooking and heating (Smith-Sivertsen et al. 2009). Smoking is considered as another major factor for causing COPD (Fortoul et al. 2011). PM and NO_x have shown strong association with the development and worsening of the existing COPD (Salvi and Barnes 2009). PM matter released after the combustion of fuel enters into the lungs via airways causing inflammation and impairment of the lung function by increasing the permeability of endothelial cells, activating macrophages, lymphocytes $CD8^+$ and neutrophils (Fortoul et al. 2011). PM can also carry microorganisms which get adhered on the surface of air passage cavity and lungs which may exacerbate the prevalence of COPD (Sethi and Murphy 2001; Sze et al. 2014; Ni et al. 2015).

10 $\mu g/m^3$ increase in the concentration of PM_{10}, O_3, NO_2, and SO_2 in ambient air also elevates the risk for prevalence and hospital admission because of COPD (Ghozikali et al. 2015; Khaniabadi et al. 2018). Næss et al. (2007) have shown that increase in NO_2 levels of more than 40 $\mu g/m^3$ increases the prevalence of COPD in individuals of two different age groups: 51–70 and 71–90 years.

Heavy metals are also known to worsen the COPD (Leem et al. 2015; Heo et al. 2017). Studies performed in animal models of COPD or emphysema have shown that to trigger the inflammatory response in lungs along with the progression of emphysema upon intratracheal injection or inhalation of cadmium, similar symptoms are observed in COPD patients (Thurlbeck and Foley 1963; Tuder et al. 2003; Kirschvink et al. 2005, 2009). High concentration of various trace metals such as cadmium, cobalt, iron, and mercury is found in high concentration of the serum of COPD patients compared to the control (Asker et al. 2018; Heo et al. 2017). Another large-scale study performed in the United States found positive correlation between cadmium and lead concentration in serum with the occurrence of obstructive lung disease (OLD) and reduced lung function (Rokadia and Agarwal 2013).

7.5.3 Pulmonary Carcinogenesis and Mutagenesis

Lung cancer is one of the major causes of death across the globe (Torre et al. 2015). Earlier, consumption of tobacco in any form, either chewing or smoking was considered as prime cause of cancer. It has been known that 90% of lung cancer deaths in male and 75–80% lung cancer deaths in female in the United States are solely attributed to tobacco smoking (Hecht 1999). Although high number of lung cancer cases are also found among nonsmokers as well (Beelen et al. 2008; Raaschou-Nielsen et al. 2010), this indicates that there are other factors apart from tobacco consumption which are responsible for lung cancer. These factors can be environmental tobacco smoke, occupational and environmental exposure to

carcinogens or mutagens (such as radon, arsenic, lead, or mercury), exposure to smoke emission from industries and traffic (Nyberg et al. 2000). A number of studies have been performed independently and they established a strong correlation between air pollution and lung cancer mortality. On the basis of one of the largest studies performed in Europe, urban air pollution is responsible for contributing as high as 11% in lung cancer cases (Molina et al. 2008). Another study performed in six different states of the United States found positive association between the air pollution and the mortality rate because of lung cancer and cardiopulmonary disease (Dockery et al. 1993). Increase in the ambient concentration of $PM_{2.5}$ for more than 10 μg/m^3 increases the risk of lung cancer mortality up to 8% (Perez-Padilla et al. 2010; Pope et al. 2002).

PMs generated from heavy metals such as lead (Pb), mercury (Hg), nickel (Ni), cadmium (Cd), cobalt (Co), and chromium (Cr) are known to have carcinogenic effects on human and animal models. They are considered as driving forces for lung carcinomas (Salnikow and Zhitkovich 2008). These heavy metals interfere the vital functions of human body at the cellular and molecular level by deregulating the cell proliferation, differentiation, or apoptosis. Cadmium modulates the gene expression and signal transduction and alters the levels of the different proteins involved in the cellular defense mechanism such as DNA repair and cell death (Matés et al. 2010). Cadmium and cobalt both trigger the lung carcinomas in animal models upon inhalation (Beyersmann and Hartwig 2008). Nickel has also been recognized as a potent carcinogen. In several animal studies inhalation of particulate nickel caused tumor development in lungs (Dunnick et al. 1995). It causes epigenetic status of the DNA which in turn alters the gene expression pattern, disrupting the iron homeostasis in cells and the function by binding with the iron-dependent enzymes, generating Reactive Oxygen Species (ROS) and hypoxic-signaling pathways into the cells (Salnikow and Zhitkovich 2008). Cr is another heavy metal known to possess carcinogenic and mutagenic abilities. Upon entering into the cells the reduction of Cr takes place from Cr(IV) to Cr(III) which can cross-link between different macromolecules such as DNA–DNA or DNA–Protein (Fortoul et al. 2011). Feng et al. (2003) found that lung cancer from workers exposed to Cr(IV) at occupational site carries a very high percentage of Guanine (G) to Thymine (T) transversion mutation in the non-transcribed strand of p53 gene in lung tissues. p53 is a tumor-suppressor gene. Direct and long-term exposure to cadmium elevates the risk of developing lung cancer (Tchounwou et al. 2012).

Gaseous pollutants such as SO_x and NO_x have been associated with lung cancer. Inhalation of these pollutants such as ultrafine and fine particulate, SO_x can cause DNA damage which can ultimately lead to lung cancer (Cao et al. 2011). Compare to the 30 μg/m^3 (lowest exposure level) of NO_x exposure, increase in the incidence rate ratio of lung cancer were 1.30 (95% CI; 1.07-1.57) for 30-72 μg/m^3 (Intermediate exposure level) and 1.45 (95% CI; 1.12-1.88) for >72 μg/m^3 (highest exposure level) of NO_x. Corresponding to that, there is 37% (95% CI; 6-76%) elevation in the lung cancer incidence rate ratio per 100 μg/m^3 of NO_x exposure has been observed (Raaschou-Nielsen et al., 2010).

7.6 Cardiovascular System

Out of the total deaths caused by air pollution, around 60–80% is because of cardiovascular diseases (Lelieveld et al. 2015). Exposure to different pollutants can cause different types of damage and affect the cardiovascular health differently. Numerous studies have established a strong correlation between particle pollution and blood pressure and it is well known that increase in blood pressure increases the risk of cardiovascular diseases (Ibald-Mulli et al. 2001; An et al. 2018). Short-term exposure to air pollution can provoke acute effects such as fluctuation in blood pressure and long-term exposure can escalate the risk of cardiovascular disease and can also reduce the life span by a few years (An et al. 2018). Cardiovascular health is mainly affected by oxidative stress, systemic inflammation, and autonomic nervous system imbalance that affect arterial walls (Krishnan et al. 2012).

7.6.1 Blood Pressure and Hypertension

A number of studies assessing the effect of air pollution on cardiovascular morbidity and mortality had also monitored the fluctuation in the blood pressure. It has shown that there is increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 2.8/2.7 mm Hg in patients after rise in the levels of $PM_{2.5}$ per 10 μg/m^3 (Brook 2007). Exposing 23 non-smoking, healthy individuals to $PM_{2.5}$ and ozone (O_3) for 2 hrs. showed a significant rise of 6 mmHg in DBP (Urch et al. 2005). A study carried out with random population of more than 3000 sample size found that there is 0.74 mmHg (95% CI: 0.08–1.40) increase in SBP with an elevation in the level of SO_2 by 80 μg/m^3 (Ibald-Mulli et al. 2001). A study conducted by Guo et al. (2010) in Beijing, China indicates that 10 μg/m^3 increase in the concentration of SO_2 and NO_2 is associated with increase in the number of Emergency Hospital Visits (EHVs), hence concluding that increase in the gaseous pollutant is associated with hypertension-related EHVs.

The association between exposure to heavy metals such as mercury (Torres et al. 2000; Clarkson et al. 2003; Houston 2011), lead (Harlan 1988; Bogden et al. 1991; Vaziri et al. 1999), cadmium (Gallagher and Meliker 2010), arsenic (Abhyankar et al. 2012; Alissa and Ferns 2011) and increase in the blood pressure or hypertension has been well established. Study performed in Bangladesh has established the dose-dependent relationship between the high prevalence of hypertension among the locals living in the endemic areas and high arsenic levels in the water bodies compare to those living in non-endemic areas (Rahman et al. 1999). It has been shown that high levels of cadmium in blood is associated with modest elevation in the blood pressure; however, no association was found between urinary cadmium levels and blood pressure (Tellez-Plaza et al. 2008). Association between lead exposure and hypertension is well established by numerous studies (Pirkle et al. 1985; Harlan et al. 1985). A meta-analysis performed by Nawrot et al. (2002)

included more than 58,000 subjects; twice the increase in the concentration of lead in blood is associated with increase in SBP 0.5–1.4 mmHg and DBP 0.4–0.8 mmHg. Various independent studies have not found any consistency between different levels of mercury exposure and fluctuations in the levels of blood pressure, thereby made it difficult establish any direct relation between them (Kobal et al., 2004; Pedersen et al., 2005; Solenkova et al., 2014).

7.6.2 Systemic Inflammation and Oxidative Stress

As a result of various studies it has been known that pollutant can induce the inflammation directly in the respiratory tract which can cause systemic inflammation, hence increasing the risk of cardiovascular morbidity and mortality (An et al. 2018; Salvi et al. 1999). Exposure of individuals with concentrated ambient particles (CAP_S) (Ghio et al. 2000) and diesel exhaust (Salvi et al. 1999) initiates the local inflammation and oxidative stress with increase in the concentration of inflammatory markers such as neutrophils, B-lymphocytes, histamines, T cells (CD4+ and CD8+) in airway and bronchoalveolar lavage. With increase in the concentration of pollutants (mainly NO_2, CO, and PM_{10}) increase in the levels of plasma fibrinogen and viscosity has been observed, possibly due to the inflammatory reaction (Pekkanen et al. 2000; Peters et al. 1997). A study performed in animals where adult mice were co-exposed with different concentration of SO_2, NO_2, and $PM_{2.5}$ stimulates the inflammatory response by increasing the levels of cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), and interleukin-6 (IL-6) (Zhang et al. 2015). A control study was performed in which the healthy individuals who spent 5 days near the steel mill where the concentration of CO, SO_x, UFP was higher have shown increase in the levels of pro-inflammatory cytokines such as IL-4, IL-6, and endothelins (Kumarathasan et al. 2018).

7.6.3 Vascular Endothelial Dysfunction and Atherosclerosis

Endothelium is a single-layered wall made up of endothelial cells which line all our blood vessels, such as arteries, veins, arterioles, venules, and capillaries. It plays a critical role in maintaining cardiovascular health by regulating blood pressure, atherogenesis, and thrombosis (An et al. 2018). Short-term exposure to $PM_{2.5}$, NO_2, and SO_2 in mice causes endothelial dysfunction (Zhang et al. 2015), apoptosis in endothelial cells, increases the levels of circulating monocytes and T cells as well as antiangiogenic profile (Pope et al. 2016). A cohort study conducted in different cities indicates that increase in long-term exposure to $PM_{2.5}$ (by 3 $\mu g/m^3$) is strongly associated with 0.3% decrease in flow-mediated dilation (FMD) (95% CI: −0.6 to −0.03; $p = 0.03$) and vasoconstriction, hence affecting the endothelial function (Krishnan et al. 2012).

Studies have linked air pollution events with atherosclerosis, mechanism including lipid peroxidation and inflammation in vascular wall (Künzli et al. 2005). Vascular endothelial dysfunction is now considered as an early maker for atherosclerosis and can prognosticate future cardiovascular events (Davignon and Ganz 2004; Araujo 2011). Increase in the ambient level of $PM_{2.5}$ and traffic is positively correlated with the progression of CIMT (common carotid artery intima-media thickness), which is a biomarker and subclinical form of atherosclerosis (Künzli et al. 2010; Lorenz et al. 2014).

Paraoxonase, a HDL-associated enzyme mediated the cardioprotective antioxidant activity by hydrolyzing the oxidized lipids and trace metals such as lead, and can inhibit the paraoxonase and thus kindle the LDL oxidation and atherosclerosis development (Li et al. 2006). Animal studies have confirmed similar results where exposure of heavy metals such as lead and cadmium to the model animal leads to the progression of atherosclerosis (Revis et al. 1981; Messner et al. 2009).

7.6.4 Myocardial Infarction, Heart Failure, and Anemia

Myocardial infarction (MI) is a medical term used for heart attack, in which the flow of blood is either decreased or completely stops causing damage to the cardiac muscle. Studies have established a parallel and significant association with different pollutants such as SO_2, NO_2, PM_{10}, and $PM_{2.5}$ except O_3 and the risk of heart failure and MI (Wellenius et al., 2005b; Mustafić et al. 2012). Similar result has been observed where hospital admission and death because of heart failure is linked with the exposure of different pollutants such as SO_2, NO_2, $PM_{2.5–10}$ except O_3 (Shah et al. 2013). In a large-scale prospective cohort study and meta-analysis, annual increase of $PM_{2.5}$ and PM_{10} by 5 $\mu g/m^3$ and 10 $\mu g/m^3$ is associated with 13% and 12% increase in the incidence of acute coronary events (MI and unstable angina) (Cesaroni et al. 2014).

Accumulation of mercury also occurs because of the consumption of nonfatty fresh water fish which is associated with MI as well as death from coronary heart disease (Salonen et al. 1995).

Heavy metals such as lead can be efficiently absorbed in the circulatory system that can damage the membrane of the red blood cells (RBC) by interfering with the enzymes responsible for their formation which can result in clinical anemia (Nikolić and Nikić 2008). Chronic exposure to air pollution can cause anemia in humans (WHO 2000). A meta-analysis study reported about 13% increase in the cardiovascular mortality rates after 10 $\mu g/m^3$ increase in the NO_2 concentration annually (Faustini et al. 2014).

7.7 Nervous System

Correlation between air pollution and respiratory health has been well described by countless independent studies across the globe. From last few years, studies have shown that retrograding quality of air causes oxidative stress and inflammation which is then transmitted beyond lungs and vascular system causing damage to the central nervous system (CNS) (Sunyer 2008). Air pollution assaults the nervous system in many different ways either by causing the damage at cellular and molecular level, activating multiple pathways involved in inflammation and oxidative stress which leads to neurological disorders. Pollutants such as PAH, $NO_{x,}$ lead, and mercury are considered as major neurotoxicant. Long-term exposure to such pollutants can lead to neuro-developmental defects. Animal studies have shown that exposing the animals to high levels of pollution, such as PM, combustion, and smoke from diesel engine resulted in accumulation of pro-inflammatory cytokines in brain tissue (Guxens and Sunyer 2012). There is a strong correlation between inflammation and neurodegradation. While breathing tiny nanosized particles can move into the CNS causing neuro-inflammation, oxidative stress and neurotoxicity (Block and Calderón-Garcidueñas 2009; Levesque et al., 2011). Air pollution is known to affect *in utero* growth and postnatal development.

Two hypotheses explain how air pollution affects the nervous system (Sunyer 2008; Guxens and Sunyer 2012):

1. *Indirect affect*: Inflammation in the respiratory tract alters the levels of cytokines, e.g., TNF-α and IL-1, which upregulate the expression of two important inflammatory genes in brain COX2 and IL-1β.
2. *Direct affect*: It has been observed that ultrafine particles containing metals translocate directly into the brain without entering into the respiratory tract.

7.7.1 Neuro-inflammation, Oxidative Stress, and Neurotoxicity

In vitro experiments performed on cells, where they are dosed with laboratory-generated or filter-collected ambient UFPs showed varied degree of pro-inflammatory and oxidative stress-related cellular response and decreased cell growth and viability (Oberdörster et al. 2005). Another in vitro study has established a dose-dependent relationship between the exposures of astroglial cells with oxygen-ozone. 0–40 μg/mL of oxygen-ozone gas per mL of complete medium were not toxic to astroglial cells, while higher concentrations 60 μg/mL or more severely decreased cell viability (Zhou et al. 2008). Oberdörster and Utell (2002) suggested that brain may be vulnerable with the exposure to UFP.

A study was conducted in which rats were exposed to diesel exhaust that demonstrated the uplifted levels of various inflammatory cytokines such as IL-6,

IL-1β, MIP-1 (macrophage inflammatory factor), and TNF-α (Levesque et al. 2011). Another study has shown that young adults aged 25.1 ± 1.5 years from high exposure to air pollution have upregulated cyclooxygenase-2 (COX-2), IL-1β, and CD14 in olfactory bulb, substantia nigrae, frontal cortex, and vagus nerve as well as disrupting the blood–brain barrier, generating oxidative stress, and inflammatory cell trafficking compared to the group who were less exposed to air pollution (Calderón-Garcidueñas et al. 2008).

Heavy metals such as lead, mercury, and manganese are strongly implicated in neurotoxicity and nervous system damage (Block et al. 2012). Short-term exposure to lead during perinatal period and childhood has been associated with impaired intellectual function and attention, whereas high doses of lead exposure can cause encephalopathy and convulsions (Mendola et al. 2002). Chronic exposure to manganese leads to the deposition of nanosized manganese particle which causes toxicity from globus pallidus to the basal ganglia region, including the substantia nigra pars compacta involved in the Parkinson's disease (Lucchini et al. 2009). Chronic low dose exposure of ozone can induce oxidative damage and neurodegeneration in the striatum, substantia nigra, and hippocampus in rodents (Pereyra-Muñoz et al. 2006; Rivas-Arancibia et al. 2010). Another study in rats has shown that when exposed to carbon monoxide there is elevation of oxidative stress in cochlear blood vessels which in turn destroys the spiral ganglia neuron and inner hair cells (Lopez et al. 2008).

7.7.2 Neurological Disorder and Neuropsychological Effects

New evidences are emerging from different studies suggesting that increase in the ambient air pollutants increases the risk of getting different neurological disorder such as stroke, Multiple Sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD) in adults (Genc et al. 2012). AD is one of the most prevalent causes of dementia and chronic neurodegenerative disorder which gradually worsens with time. It is characterized by either the deposition of amyloid-beta (Aβ) peptide fibrils known as amyloid plagues or the tangles of another twisted protein called Tau built up inside the cells (Ballard et al. 2011). The second most common neurodegenerative disorder is Parkinson's disease. PD is associated with gradual loss of dopaminergic loss of neurons in the substantia nigra which results in the dysfunction of basal ganglia that is responsible for the initiation and execution of the movements (Shulman et al. 2011). The occurrence of neurodegenerative disorder is governed by multiple factors including genetic predisposition, nutritional factors, and environmental factors such as exposure to heavy metals and chemicals (insecticides, pesticides) and air pollution (Migliore and Coppedè 2009). There are some common factors which can trigger or contribute in the onset of neurological disorders by damaging the specific neurons such as protein aggregation and amyloid formation, oxidative stress and inflammation in neuronal cells, mitochondrial dysfunction,

cellular apoptosis, and microglial activation (Ballard et al. 2011; Shulman et al. 2011).

Many epidemiological studies have shown adverse effects of air pollution on the cognitive behavior in elderly adults (Kramer et al. 2009; Power et al. 2011). Long-term exposure to $PM_{2.5}$ and PM_{10} is cognitively equivalent to brain aging by 1–2 years and is associated with significant decline in the cognitive function in older women (Weuve et al. 2012; Chen et al. 2015). It has been found that young adults and children living in cities with high air pollution levels have altered brain innate immune response and accumulation of Aβ42 and α-synuclein in their neurons (Calderón-Garcidueñas et al. 2008). Exposure to mercury can affect the CNS differently depending on the exposure. Individuals exposed to mercury vapor have impaired cognitive abilities, mainly affecting memory, attention, and psychomotor functioning (Milioni et al. 2017).

Another animal study in which rats were exposed to ozone for a short period resulted in the development of cerebral edema (Crețu et al. 2010). Behavioral studies in rats showed that exposure to ozone can alter the behavior depending upon the dose, time of exposure, and stage of development (Rivas-Arancibiaa et al. 2003; Santucci et al. 2006; Sorace et al. 2001).

7.7.3 Stroke

A stroke is known to occur when the blood supply to different parts of brain is disrupted or reduced, depriving the brain from essential components to function such as oxygen and nutrients. Depending on the cause, strokes have been classified into two categories: Ischemic stroke and Hemorrhagic stroke. Ischemic stroke is solely responsible for 80% of total deaths caused by stroke in which blood supply to the brain tissues gets impaired because of the clot formation and for the rest 20% of stroke deaths is because of hemorrhagic stroke, in which there is a leakage of blood from vessels around the brain (Villeneuve et al. 2006). It has been clearly understood that increase in the ambient air pollution causes inflammation which elevates the level of various cytokines in the blood that promote blood coagulation and thrombosis (Seaton et al. 1995). From the last few years many epidemiological studies have been performed independently providing compelling evidences between the quality of air and the stroke mortality.

While breathing, CO enters into the lungs where it binds with hemoglobin in the blood instead of oxygen and forms carboxy-hemoglobin (COHb), which interferes with the transport of oxygen which may result in hypoxia, neurological disorder, and neuropsychological alterations (Schwela 2000). Villeneuve et al. (2006) showed that CO and NO_2 exposure is associated with the increased risk of hemorrhagic stroke (ORs 1.32, 95% CI = 1.09–1.60) and (ORs 1.26, 95% CI = 1.09–1.46). In 2003 Tsai et al., found a positive correlation between different pollutants and stroke incidences, from the data collected in the span of 4 years from 1997 to 2000. In the single-pollutant model, a positive relationship is established between levels of different

pollutants such as SO_2, NO_2, CO, O_3, and PM_{10} and hospital admissions because of both ischemic stroke and primary intracerebral hemorrhage whereas in the 2-pollutant models, only PM_{10} and NO_2 are significantly associated and correlated with hospital admissions for both the types of stroke wherein the effects of CO, SO_2, and O_3 gaseous pollutants were mostly nonsignificant when either NO_2 or PM_{10} levels were controlled independently (Tsai et al. 2003). Another study that describes the similar finding where, increase in the stroke mortality cases for each interquartile range in the same day was 1.5% [95% CI, 1.3–1.8%] for PM10 and 2.9% (95% CI, 0.3–5.5%) for O3 wherein, increase for each interquartile range in a 2 day lag was 3.1% (95% CI, 1.1–5.1%) for NO2, 2.9% (95% CI, 0.8–5.0%) for SO2, and 4.1% (95% CI, 1.1–7.2%) for CO (Hong et al. 2002a). Many other independent studies have confirmed similar findings, stating that stroke cases are significantly associated with prevailing levels of NO and O_3 (Wellenius et al. 2005a; Maheswaran et al. 2005; Hong et al. 2002b). Symptoms of stroke and other cerebrovascular diseases can be instigated by the pollutants in much lower concentration than given as guidelines in many different countries and the world health organization (WHO) (Ponka and Virtanen 1996).

7.8 Digestive System

Effect of air pollution on digestive system has been least studied when compared with a number of studies performed to analyze the effect of ambient air pollution on respiratory system or cardiovascular system. Oral route is usually exposed to more pollutants present in air, as both food and water are affected significantly by the quality of air. All the particles >6 μm get clear from the lungs with mucus and transported to the intestine. Pollutant in the air can cause intestinal injury by directly affecting the epithelial cell layer, increase in the immune response and amending the gut flora (Opstelten et al. 2016). Systemic inflammation caused upon exposure to different pollutants affects intestine as well as is responsible for other gastric disorders.

7.8.1 Inflammatory Bowel Disease (IBD) and Appendicitis

New studies have found a positive correlation between the air pollution levels and gastrointestinal disorders such as Inflammatory Bowel Disease (IBD) and appendicitis. With increase in industrialization, there is increase in the incidence of Ulcerative Colitis (UC) and Crohn's disease; despite this fact, fewer studies are available which studied the direct effect of air pollution and IBD.

It has been seen that there is increase in the incidences of UC and Crohn's disease in the developed nations of North America and Western Europe (Richard F.A. Logan 1998). However, there were rare cases of IBD that were observed in developing

nation such as India and China, but with the boom in industrialization, there is increase in the incidences of IBD (Desai and Gupte 2005; Zheng et al. 2005). Both UC and Crohn's disease are considered as two major forms of IBD. On the whole, the incidence of the IBD occurrence is not related directly with air pollution but children and young adults living in areas with high concentration of SO_2 and NO_2 are more likely to suffer from ulcerative colitis and Crohn's disease (Kaplan et al. 2010). Another study performed in 2011 by Ananthakrishnan et al. found that there is a strong association between the hospitalization cases due to the IBD (3890 cases, mean of 81.3 IBD hospitalizations/100,000 people per year) with increase in the pollutants.

There is a dramatic surge in the cases of appendicitis recorded during the nineteenth and early part of the twentieth century when the industrialization of the society was at its peak (Williams 1983). Later in the middle of the twentieth century many countries such as the United States and the United Kingdom passed legislations to improve the quality of air, which resulted in significant decrease in the number of cases registered for appendicitis (Addiss et al. 1990; Chen et al. 2007; Williams et al. 1998). The strong connection between the short-term exposure to the air pollution and occurrence of appendicitis has been established (Kaplan et al. 2009). The rise in the number of appendicitis has been seen mostly during the summers, when most individuals spend their time outside exposed to pollutants like NO_2 and ozone which are considered as primary risk factors when compared to other pollutants (Kaplan et al. 2010).

7.8.2 Gastrointestinal Tumor

Gastric cancer is another most common type of cancer found globally with about twice the rate in men (Torre et al. 2015). Occupational exposure of metals and other pollutants along with dust and high temperature is associated with higher risk of developing different types or gastric/digestive system tumors (Santibanez et al. 2012; Bevan et al. 2012). The exposure of biomass smoke is associated with the frequency of gastric and oesophageal cancer (Kayamba et al. 2017). A study performed by ESCAPE (European Study of Cohorts for Air Pollution Effects) found that elevated level of $PM_{2.5}$ particles suspended in the air by 5 $\mu g/m^3$ is associated with inflation in the hazard ratio of gastric cancer by 1.38 (95% CI 0.99; 1.92) and for upper aero digestive tract cancer (UDAT) by 1.05 (95% CI 0.62; 1.77); no correlation is observed with the exposure of NO_x (Nagel et al. 2018).

A study was performed by Lopez-Abente et al. (2012) for over the period of 10 years (1997–2006), where colorectal cancer mortality cases were examined. "Near vs far" analysis of RR was estimated in those towns (total 8098) which were situated within 2 km of distance from different industrial installations. A strong and significant RR is observed in the towns situated near different industries such as mining industry (RR—1.07; 95% CI 1.00–1.14), food and beverage sector (RR—1.069; 95% CI 1.02–1.11), metal production and processing (RR—1.065; 95% CI

1.01–1.12) and ceramic industry (RR—1.05; 95% CI 1.00–1.09). Another study was performed where the risk of bladder cancer was estimated among those who work in metal industry and a positive correlation was observed (Colt et al. 2014). Similar study was performed in Spain where positive correlation was found between the risk of developing gastric tumor (colorectal and liver cancer) and residential proximity to the metal production and processing industry (García-pérez et al. 2010).

A study was performed in rats, where 7 groups of rats were fed with different concentration of DEP (0, 0.2, 0.8, 2, 8, 20, or 80 mg DEP/kg) for 21 days and DNA leisons and oxidative stress were observed causing DNA strand breakage, uplifted repair capacity of oxidative base damage, protein oxidation and cellular apoptosis in colon mucosa cells and in liver (Dybdahl et al. 2003). Exposure to cadmium and lead is positively associated with the development of prostrate, kidney, liver, and stomach cancer (Tchounwou et al. 2012; Rousseau et al. 2007; Steenland and Boffetta 2000).

7.9 Effect on Fertility, Reproduction, and Pregnancy

From the last two decades scientists have been debating over the impact of air pollution and infertility. There are many studies performed which claimed that there is no association between the amount of pollutants in the ambient air whereas in retrospect many other studies found a positive correlation between infertility, childbirth, and quality of air. WHO has concluded that the increase in the levels of air pollution has adverse effects on pregnancy (WHO 2005). Although different pollutants exert varied effects when exposed to them either independently or in combinatorial manner.

7.9.1 Fertility

The first study in human relates to the increase in the levels of high traffic-related air pollution, particularly the concentration of coarse particle $PM_{2.5–10}$ and reduction in the fertility rates (IRR = 0.87, 95% CI 0.82, 0.94) (Nieuwenhuijsen et al. 2014). Data from epidemiological studies suggests that air pollutant damages and causes defects during the gametogenesis process which ultimately is responsible for reduction in the reproductive potentials among the exposed population (Carré et al. 2017).

Young men exposed to high concentration of SO_2 were found to have sperm abnormalities originated during the spermatid formation (Dejmek et al. 2000). With increase in concentration of $PM_{2.5}$ by 10 μg/m^3 each was associated with the decrease in fecundability of about 22% (95% CI: 6–35%), as well as high concentration of NO_2 was also associated with reduced fecundability (Slama et al. 2013). More than 40 μg/dL of inorganic lead in the blood can impede male reproductive function by impairment in spermatogenesis, reduction in sperm count, volume and density as well as change in sperm mobility and morphology (Apostoli et al. 1998).

In a prospective cohort of nurses, small increase in the risk of infertility was observed among individuals living close to the major roads compared to those who are living far away from the major road (multivariable hazard ratio 1.11, 95% CI 1.02–1.20) (Mahalingaiah et al. 2016).

7.9.2 Fetus Development, Child Birth, and Development

Fetus development is a critical stage that is more vulnerable to the toxic pollutant because of rapid cell division and proliferation, development of organs and less pronounced metabolic pathways (Srám et al. 2005). A study carried out in Sydney stipulate that 10% reduction in the ambient concentration of $PM_{2.5}$ for over 10 years resulted in about 650 (95% CI: 430–850) fewer premature deaths (Broome et al. 2015). A time-series study conducted in Vancouver analyzed the effect of gaseous pollutant on different stages of pregnancy and child development. They found that the exposure to the elevated level of SO_2 during the first month of pregnancy resulted in low birth weight of the child whereas exposure to SO_2 and CO in the last month of pregnancy resulted in the preterm birth and along with NO_2 was also responsible for intrauterine growth retardation (IUGR) of the developing fetus (Liu et al. 2003). A strong association was observed between SO_2 and preterm birth and low birth weight, whereas levels of total suspended matter (TSP) and NO_x show weak correlation and marginal correlation (Bobak 2000). Another attempt was made in Southern California to study the effect of pollutants such as CO, SO_2, NO_2, O_3, and PM_{10}. With increase in the concentration of PM_{10} by 50 μg over 6 weeks results in 20% preterm birth although the levels of CO and number of preterm birth was not consistent, and hence, no pattern was observed (Ritz et al. 2000). Pre- or postnatal exposure to PAH, $PM_{2.5}$, and NO_x can delay or wield the negative effect on the neuropsychological development in children (Frutos et al. 2015). Exposure to lead is strongly associated with decline in intelligence, less IQ (Intelligent Quotient), retardation in neurobehavioral development, impairment of hearing and speech, and poor attention and growth (Amodio-cocchieri et al. 1996; Kaul et al. 1999; Tchunwou et al. 2012).

7.9.3 In Vitro Fertilization (IVF), Clinical Pregnancy, and Implantation Rates

There are very few studies in literature demonstrating the effects of air pollution on IVF (Frutos et al. 2015). Studies have reported the pernicious effect of elevated level of air pollutants on clinical pregnancy and implantation rates (Perin et al. 2010a, b).

Legro et al. (2010) studied the effect of different pollutants at different stages of IVF and embryo transfer. Increase in the concentration of NO_2 is significantly related

to the reduction in the probability of conceiving pregnancy and live birth during all the stages of an IVF cycle with OR—0.76 (95% CI: 0.66–0.86), per 0.01 ppm increase. Increase in the concentration of O_3 was negatively associated with live birth but the association was not significant. No correlation was observed between the levels of SO_2 and PM_{10} and live birth rate, number of oocytes retrieved and embryo transfer to the women undergoing their first IVF cycle.

7.9.4 Miscarriage

Green et al. (2009) concluded that pregnant women living within 50 m of road are at high risk of spontaneous abortion because of traffic and vehicle emission. Another epidemiological study performed in Labin (Croatia) found significant association between the pollutants released from the combustion of coal and complications during pregnancy, miscarriages, and stillbirths (Mohorovic et al. 2010). It was also observed that there is more than twofold increase in the risk of miscarriage when there was a brief exposure to high levels of PM_{10} during the preconceptional period irrespective of the method of conception (Perin et al. 2010a, b). Another study performed by the same group confirms the above finding where women exposed to high concentration of PM (>56 μg/m^3) during the follicular phase of conception cycle had high risk of miscarriage (OR—5.05; 95% CI: 1.04–25.51) (Perin et al. 2015). Faiz et al. (2012), examining the rate of stillbirth associated with air pollution levels from 1998 to 2004, confirmed that increase in the levels of different gaseous pollutants such as NO_2, SO_2, and CO during pregnancy appeared to increase the relative odds of stillbirth. They showed that 10-ppb increase in concentration of NO_2 during the first trimester (OR = 1.16, 95% CI: 1.03–1.31), 3-ppb increase in the concentration of SO_2 during the first (OR = 1.13, 95% CI: 1.01–1.28) and third (OR = 1.26, 95% CI: 1.0–1.37) trimesters, and each 0.4-ppm increase in concentration of CO during the second (OR = 1.14, 95% CI: 1.01–1.28) and third (OR = 1.14, 95% CI: 1.06–1.24) trimesters is associated with relative odds of stillbirth.

Exposure to heavy metals such as lead from low to moderate concentration (0–30 μg/dL) elevates the risk of spontaneous abortion (Hertz-Picciotto 2000).

7.10 Effect on Skin

Skin is the first line of defense in the body of an organism; being the largest and outermost organ, it is exposed to all the pollutants present in the environment. Air pollutants exist in many different forms and hence can directly cross the physical barrier and be absorbed by the subcutaneous tissue and sebaceous glands present beneath the skin. Prolonged exposure of the skin to the pollutants can alter its normal defense mechanism and exert a detrimental effect which may result in various skin

diseases (Puri et al. 2017). There are four mechanisms through which air pollutants can cause adverse effects on skin health (Mancebo and Wang 2015):

- Free radical generations
- Induction of inflammatory signaling cascade and subsequent impairment of skin barrier
- Aryl hydrocarbon receptor (AhR) activation
- Alteration in skin microflora

Encounter of various pollutants with the skin can cause oxidative stress which destroys the homeostasis by depleting the cellular pool of redox enzymes (glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase) and antioxidants (Vitamin E, Vitamin C, and glutathione) (Valacchi et al. 2012). Oxidative stress can cause alteration in the activation status of a number of transcription factors (AP1, NF-kB, cJUN, etc.) and rewiring various generic signaling pathways such as ERK-1/2/5, p38, and JNK (Wlaschek et al. 2001; Dhar et al. 2002; Kim et al. 2005) resulting in the damage of macromolecules (DNA, proteins, or lipids), extrinsic aging of the skin, inflammatory or allergic reactions such as dermatitis (contact or atopic), psoriasis, acne, and skin cancer (Kampa and Castanas 2008; Baudouin et al. 2002; Kohen and Gati 2000; Halliwell and Cross 1994).

7.10.1 Oxidative Stress, Skin Aging, and Pigmentation

PAH gets converted into quinones, redox-cycling chemicals that can generate reactive oxygen species (ROS) (Penning 1993). PAH can bind to the combustion-derived PM in the air which can be readily absorbed in the skin by hair follicle or trans-epidermal absorption and result into oxidative stress and skin aging (Menichin 1992; Vierkotter et al. 2010). A direct correlation between prevalence and severity of acne and the number of cigarettes smoked among smokers has been observed (Schäfer et al. 2001). PAH is known to be associated with skin aging and pigmentation (Puri et al. 2017). Long-term exposure of murine skin to ozone diminishes the levels of antioxidants such as tocopherol (vitamin E) and ascorbic acid (vitamin C) and elevates the level of lipid peroxidation product (malondialdehyde) which impair the normal functioning of skin cells and causes inflammation (Thiele et al. 1997).

Exposing normal human epidermal keratinocytes (NHEKs) to 0.8 ppm ozone for 30 min will result into DNA damage, depletion of ATP levels, NAD-dependent histone deacetylase, sirtuin3. (McCarthy et al. 2013). Similar levels of ozone's exposure to human participants resulted in 70% decrease in the endogenous levels of vitamin E and increase in the levels of lipid hydroperoxide by up to 230% in stratum corneum (He et al. 2006). Direct exposure of skin to dust particles, cigarette smoke, oxides (SO_x, NO_x, O_3) and VOCs results in oxidative damage, significant increase in the levels of pro-inflammatory genes and also the genes responsible for wrinkle formation, pigmentation and aging (Choi et al. 2011; Krutmann et al. 2014)

Long-term exposure to particulate matter can lead to pigmentation, which is the sign of premature skin aging (Vierkotter et al. 2010; Krutmann et al. 2014).

7.10.2 Dermatitis, Psoriasis, and Eczema

Schultz-Larsen (1993) found that the pervasiveness of atopic dermatitis has increased over the past few decades in Europe. A comparative study was performed in different parts of Germany examining different parts and levels of pollution such as East Germany (industrial; sulfurous) and West Germany (urban; oxidizing), which showed that the prevalence of atopic dermatitis was greatest in East Germany when compared to West Germany as well as many other direct and indirect parameters of air pollution were measured and the greatest association of the atopic eczema was found with NOx exposure (indoor use of gas without the cooker top and close proximity to roads with heavy traffic) (Schäfer and Ring 1997).

A study performed in children when shifted from one building to another during study indicated that there is increase in the risk of atopic dermatitis aggravation due to high levels of VOCs in the building (Kim et al. 2015). Exposure of keratinocytes cultures with VOCs are known to elevate the concentration of various cytokines such as IL-8 and IL-1B causing atopic dermatitis and eczema (Puri et al. 2017). NO_2, SO_2, and SO_3 were associated with exacerbation of eczema and atopic dermatitis whereas $PM_{2.5}$ has higher heavy metal ratio (such as arsenic, copper, cadmium, nickel, vanadium, lead, and zinc) compared to PM_{10}, and is associated with prevalence of eczema and atopic dermatitis (Kathuria and Silverberg 2016). An increase in the concentration of ozone by 10 $\mu g/m^3$ in 7 days average resulted in significant increase in the urticaria (3.84%), eczema (2.86%), contact dermatitis (3.22%), and rash (2.72%) (Xu et al. 2011).

Kramer et al. (2009) showed that children of age 6 years living in traffic-related, highly polluted areas are at greater risk for the prevalence of eczema (risk of 1.69 per 90% range of soot concentration).

7.10.3 Skin Cancer

Melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) are the most common types of skin cancer in people worldwide. In an animal study VOCs (hexachlorobenzene) have seen to cause precancerous lesion on the skin of rats (Michielsen et al. 1999). Activated PAH can produce epoxides and diols which can bind to the DNA and are responsible for causing carcinogenesis (Baudouin et al. 2002; Kelfkens et al. 1991). A meta-analysis showed that smoking was significantly associated with cutaneous squamous cell carcinoma and basal cell carcinoma (OR, 1.52; 95% CI, 1.15–2.01 and OR, 0.95; 95% CI, 0.82–1.09) or nonmelanoma skin cancer (OR, 0.62; 95% CI, 0.21–1.79) (Leonardi-Bee et al. 2012). Rezazadeh and

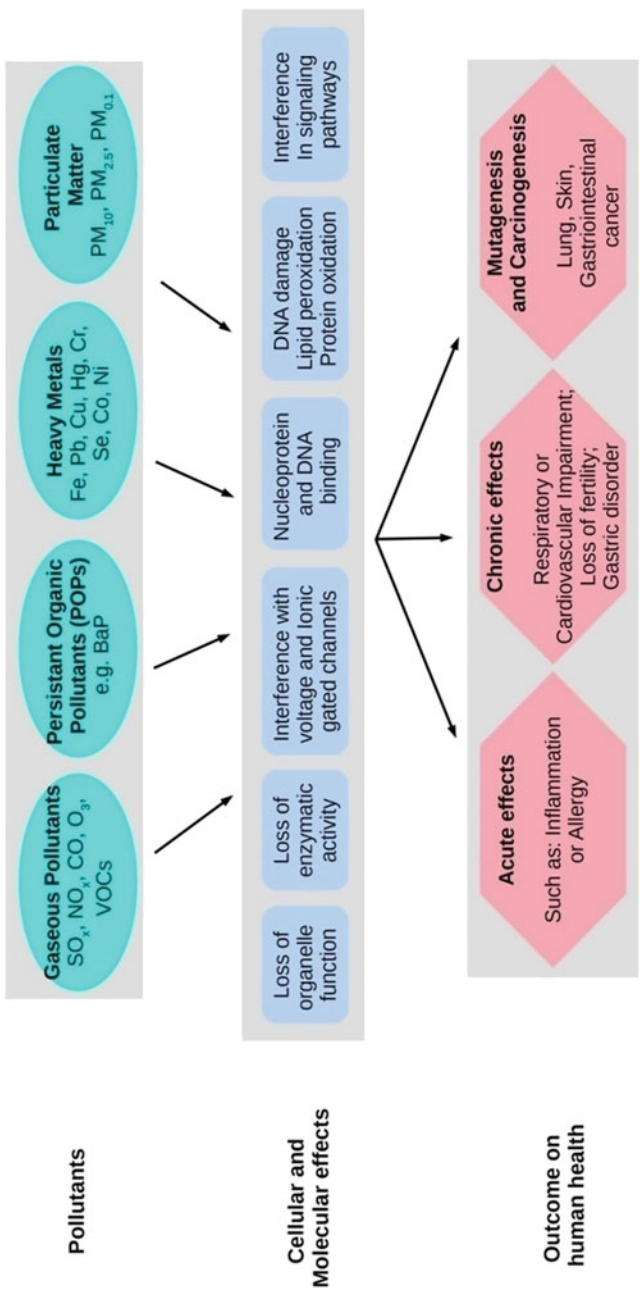

Fig. 7.2 Mechanism by which pollutants affect human health

Athar (1997) showed that the iron overload on 7,12-dimethylbenz[a]anthracene promotes genotoxic stress and initiates skin tumorigenesis in mice. Ingesting arsenic alone or in combination with other risk factors such as UV-B, it is known to cause SCC and BCC (Fabbrocini et al. 2010).

7.11 Summary

This chapter reviews the adverse effects of different air pollutants on human health. Pollutants in air can trigger and exacerbate many diseases which may affect many different organs and systems by impairing their ability to perform normal function, ultimately leading to high mortality and morbidity. As mentioned, concentration of pollutants and exposure time cause different acute and chronic effects. Briefly, Fig 7.2 summerizes different pollutants and their effects of different systems and organs of human body.

It has been over five decades when the first study about the effect of environmental pollutants on human health was performed; it is still one of the major topics of research in the area of environmental science and human health. Dose-dependent effects of many pollutants have been studied extensively for different body systems and organs, such as pulmonary or cardiovascular system. Other systems and organs such as digestive system, nervous system or in skin, the effects of air pollution has been overlooked, though few studies were performed which established a strong and direct correlation between them. Controlled exposure studies of toxic air pollutants solely cannot explain the effects of air pollutants on human health; along with that animal toxicology, occupational and epidemiology studies together can conclude the effect of a single pollutant and complex pollutants on human health.

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