



Particulate matter air pollution and respiratory impact on humans and animals

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Abstract

Air pollution is now fully acknowledged to be a public health problem and a social issue. Particulate matter (PM) concentration has been linked with several clinical manifestations of pulmonary and cardiovascular diseases and is associated with morbidity and mortality induced by respiratory diseases both in human and animals. Current research on airborne particle-induced health effects investigates the critical characteristics of particulate matter that determine their biological effects. Scientific evidence assessed that the size of the airborne particles and their surface area determine the potential to elicit inflammatory injury, oxidative damage, and other biological effects. Thus, the present review paper aims to summarize the current evidences and findings on the effect of air pollution on lung function in both humans and animals.

Keywords Particulate matter · Public health · Environment · Air pollution · Biomolecular · Morphopathology

Introduction

In the last decades, a growing number of studies have been shown that air pollution causes adverse health effects. The extensive scientific literature available on this topic include epidemiological, clinical, and toxicological studies that have systematically documented a wide range of health outcomes, from respiratory symptoms to cardiopulmonary cause of mortality and lung cancer (Pope III and Dockery, 2006; Pascal et al. 2013; WHO 2013; Beelen et al. 2014; Mannucci et al. 2015). Various reports showed that air pollution has also been associated with health impacts on fertility (Somers, 2011), pregnancy (Dadvand et al. 2013; Proietti et al. 2013), newborns, and children (Bosetti et al. 2010; Sapkota et al. 2012; Stieb et al. 2012). There is emerging evidence that the exposure to air pollution may lead to negative effects on neural development and cognitive capacities (Oberdorster et al. 2004; Weuve et al. 2012; Guxens et al., 2014), as well as, with new-onset type 2 diabetes in adults (Kramer et al. 2010; Puett

et al. 2011; Janghorbani et al. 2014), and it may be linked to obesity, systemic inflammation, aging, Alzheimer's disease, and dementia (RCP 2016, and references therein; WHO 2016). Moreover, climate changes induced by air pollution may interfere with livestock activities in many species (Pagabeleguem et al. 2012; Martí-Herrero et al. 2015; Bouyeh et al. 2017).

Health outcomes are mainly observed at pollutants concentrations which are exposed urban populations in both developed and developing countries (WHO 2013; EEA 2017). Clinical and toxicological studies have provided significant information on the effects of specific pollutants and on the possible mechanisms underlying these effects, reinforcing the plausibility of the associations observed in epidemiological studies.

In 1970s, the American Clean Act (CAA) laid the basis of current air pollution legislation by defining the air quality standards as well the limits of major pollutants involving in public health problems such as PM, carbon monoxide, iron, ozone, sulfur dioxide, and nitrogen dioxide (NAAQS. National Ambient Air Quality Standards, 2011).

According to latest analysis of EEA (2017) in large parts of Europe, the concentrations of PM continued to exceed the EU limit values. In 2015, a total of 19% of the EU-28 urban population was exposed to PM10 levels above the daily limit value and approximately 53% was exposed to concentrations exceeding the stricter WHO AQG (Air Quality Guidelines)

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value for the same pollutant. In the period 2000–2015, the same agency referred that between 16 and 43% of the total urban population was exposed to PM₁₀ levels above the limit values (EEA 2017).

The environmental monitoring networks and the epidemiologic studies allow to estimate the health impact of atmospheric pollution on urban populations (EEA 2017).

In recent years, screening studies have shown that the identification and monitoring of a wide variety of environmental pollutants, that are dangerous for human health, can be assessed by surveys on animal populations called “animal sentinel systems” (SSA) (NRC 1991; Saldiva and Böhm, 1998; Van der Schalie et al., 1999; Santin et al. 2005; Peakall 2012).

Assuming that the contamination of the atmosphere causes adverse health effects in all the exposed population, sentinel species seem to be useful as potential bioaccumulators of environmental chemical agents and may be the first choice for detecting pollutants whenever there is a high affinity between pollutant and specific animal tissue (Saldiva and Böhm, 1998). Thus, both domestic and wild animals represent important biological indicators in the environmental risk assessment. The diseases connected to the action of environmental contaminants, therefore, acquire a particular meaning when the animal species, in which its presence is proven, are considered as sentinels of environmental quality.

Pathological manifestations related to exposure on toxic elements, in both wild and syntropic animal species, are important not only for the zoonotic risk but also for the use of SSA as detectors of air quality and they may be useful for predicting human health risks.

Therefore, the aim of the present review was to assess the effects of air pollution and particulate matter on human and animal health and to investigate the role of pollutants in the development of pulmonary disease.

Health impact of air pollutants: particulate matter roles

The status of air quality is an environmental emergency and a social issue that with the climate changes involves the whole population, and it concerns the local and central administrators. Although the polluting substances dispersed in the atmosphere are numerous, the evaluation of the fluctuation of PM level remains one of the most reliable measures to determine the state of environmental health; moreover, PM represents the main pollutant used to assess the health impact of air pollution (Karakatsani et al. 2012; Nemmar et al. 2013).

Epidemiological and toxicological studies have shown that PM mass (PM_{2.5} and PM₁₀) comprises different fractions and sources, determining a wide range of health effects (Kelly and Fussell, 2012). The PM is considered a complex

group of particles and dusts that carry on the surface many toxic substances and disseminating these in the air. Therefore, the PM adverse outcome includes possible effects due to other pollutants or their interactive actions (Valavanidis et al., 2008; Bell et al. 2009; Peng et al. 2009; Zanobetti et al. 2009).

The effects observed in several clinical and toxicological studies consisted in a marked correlations between airborne PM and negative impacts on respiratory and cardiovascular health (Baccini et al. 2011; Kloog et al., 2012; Raaschou-Nielsen et al. 2012; Pascal et al. 2013; Beelen et al. 2014, Cachon et al., 2014; Lu et al. 2015). Moreover, the International Agency for Research on Cancer has classified air pollution in general, and the PM as a separate component of air pollution mixtures as carcinogenic agent (IARC 2013).

Inhaled ultrafine particles seem to follow different ways in the organism; these pollutants disseminate deeply into the alveoli, allowing its diffusion through the blood–air barrier to systemic circulation and other organs. The pollution-induced health effects result in pulmonary and systemic oxidative stress and inflammation. The available findings demonstrated in fact: respiratory disease and reduction of lung function (Kelly and Fussell, 2011), local and systemic fogosis, as well as acute changes in coagulability (Franchini et al., 2012) and cardiovascular diseases (vascular dysfunction, atherosclerosis, altered cardiac autonomic function) (Simkhovich et al. 2008; Brook et al. 2010; Kelly and Fussell, 2015b; Du et al. 2016). Finally, the systemic diffusion may cause adverse effects on target organs, such as the heart, liver, and brain (Anderson et al. 2012; Karakatsani et al., 2012).

Evidences are particularly strong for long-term health effects resulting from exposure to low concentrations of atmospheric PM. The polluting particles coming to the lung parenchyma can remain there for years, generally determining pneumopathies and sclerosing pneumoconiosis (Wynn 2011; Siroux and Crestani, 2018). These effects linked the role of PM in the pathogenesis and exacerbation of a wide range of pulmonary diseases, including infectious diseases (MacIntyre et al. 2014), chronic obstructive pulmonary disease (COPD), and the reduction of lung functions (Gan et al. 2013; Jie et al. 2014).

The ultimate effect of air pollution on public health is to bring about premature death (GBD 2015). The WHO estimated that PM air pollution contributes to approximately 800,000 premature deaths each year, ranking it the 13th leading cause of mortality worldwide (EEA 2017). According to WHO, the airborne particles are responsible for 80% of cases of premature death: heart disease and stroke are the most common reasons for premature death due to air pollution; lung diseases; and lung cancer (O'Donnell et al., 2011; WHO 2014; EEA 2017). In the year 2012, WHO (2014a), referred that ambient air pollution was responsible for 3.7 million annual deaths, representing 6.7% of all-cause deaths and tripling the 2008 estimates. Worldwide, air pollution causes 16% of deaths

due to lung cancer, 11% of deaths due to chronic obstructive pulmonary disease, more than 20% of deaths due to ischemic heart disease and stroke, and 13% of deaths due to respiratory infections. In 2012, the Global Burden of Disease Report identified air pollution among the leading risk factors for disease burden, being globally responsible alone for 3.1% of disability-adjusted life years (DALY-s) (Lim et al. 2012). The causes of death were mainly related to ischemic heart disease (40%), stroke (40%), chronic obstructive pulmonary disease (COPD) (11%), lung cancer (6%), and acute lower respiratory infections in children (3%) (Kelly and Fussell, 2015a).

Particulate matter: composition and size

The PM is a portion of air pollution that is composed by extremely small particles and liquid droplets containing acids, organic chemicals, metals, and soil or dust particles. These substances can exert damaging effects to both human and environmental health, according to the contaminant's quantities being considered, the exposure time, and the harmful effects of the substance in question. PM continues to be the fraction of air pollution that is most reliably associated with human and animal disease (Anderson et al. 2012).

Composition and size of PM are associated with various clinical and toxicological effects as observed in studies conducted in vivo and in vitro on animals and humans (Zanobetti et al. 2009). These compounds, penetrated in form of aerosol, are able to modify various biological activities including the production of cytokines, the regulation of processes mediated by coagulation factors, pulmonary and cardiac function (Falcon-Rodriguez et al. 2016). For example, epidemiological and toxicological studies have reported cardiovascular disease and death linked to variations of response of cardiovascular biomarkers of systemic inflammation such as C-reactive protein and fibrinogen (Diez Roux et al., 2006; Brook et al., 2010; Kelly and Fussell, 2015a).

In addition to the complexity of its chemistry and the changing nature of the compounds within ambient air, researchers subdivided PM also by its aerodynamics equivalent diameter (AED) fractions. The size distribution of the "total suspended particles" includes the *coarse*, *fine*, and *ultrafine* fractions. The PM dimension plays an important role in animal and human defining the deposition site in the lung: coarse particles (PM10) can be accumulated in upper airways and fine and ultrafine particles (PM2.5 and smaller than 0.1 μm) can be accumulated in the lung parenchyma, inducing several respiratory and systemic diseases.

The deposition of aerosol in the lung occurs through a combination of inertial impaction, gravitational sedimentation, and Brownian diffusion (Darquenne 2014). The primary mechanism of deposition in the intrathoracic airways is

sedimentation, and therefore, the fate of these particles is markedly affected by gravity (Peterson et al. 2008). The coarse fraction (PM10–2.5) can penetrate into the upper airways (Nemmar et al. 2013), where is deposited through an impaction or sedimentation process (Darquenne 2014). The fine fraction (PM2.5) is deposited in the lung, especially in the alveoli (Nemmar et al. 2013) through sedimentation and Brownian diffusion processes (Darquenne 2014). The PM10 is deposited mainly by Brownian diffusion in the lung (Darquenne 2014) and these particles can be translocated through the systemic circulation from the lungs to liver, spleen, heart, or brain (Oberdorster et al. 2004; Kreyling et al. 2006). However, they can also arrive to the brain through the olfactory bulb by a trans-synapsis mechanism (Oberdorster et al. 2004).

Several studies have provided further evidence that the PM effects depend by its composition (Bell et al. 2009). The PM can be constituted by organic, inorganic, and biological compounds. The composition can be different among cities, depending on the predominant emission sources.

Particles with a diameter greater than 2.5 μm (coarse fraction; AED > 2.5 μm) is generated through natural process, such as natural mechanical processes of grinding, erosion, or wind mechanical re-suspension, and therefore, it is composed of elements present in the soil and in sea salts, such as silicon, aluminum, iron, calcium, potassium, sodium, manganese, and strontium. Fine particles instead originate from combustion processes (vehicles, industries, electricity production) and can be of primary origin (directly generated) or they can be formed by chemical transformation (secondary origin) from primary emissions of sulfur and nitrogen oxides (sulphates and nitrates). In industrialized areas, the major components of these fraction are sulphates, nitrates, ammonium ion, elemental carbon (black carbon), and organic carbon. Further components are represented by trace metals deriving from the combustion processes. Ultrafine particles (diameter < 0.1 μm), finally, consist of a quantity of substances with toxic properties adsorbed on its surface (so-called micro-pollutants) like the products of supersaturated vapors (sulfur dioxide, ammonia, nitrogen oxides) and combustion products. This form of particulate represents the greatest concerns about the impact on health in both the scientific community and the environmental surveillance agencies. The ultrafine particles in fact carry on its surface a mixture of chemical compounds potentially more toxic than the sole particle. These molecules, adsorbed on the surface of the particles, also present a longer residence time in the lung parenchyma (Kelly and Fussell, 2015a; Falcon-Rodriguez et al. 2016). Growing evidences underlying the biological basis of toxicity of this fraction and its aerodynamic behavior characterized by direct involvement of the deeper lung compartment and the subsequent deposition of substances with more dangerous toxicological outcome (HEI 2013; Kelly and Fussell, 2015a). In PM2.5, the presence

of organic (IPAs, > 90%) and inorganic (heavy metals, asbestos fibers) components was also observed. Chemical analysis of the inorganic fraction shown that in PM_{2.5}, ammonium sulphates and nitrates account for over 40% of the collected particulate. Therefore, the inhalation of fine particles is accompanied by the introduction of more dangerous substances, such as carcinogenic hydrocarbons and heavy metals.

In fact, the organic compounds of PM have mutagenic and cytotoxic properties contributing to various mechanisms of cytotoxicity. In addition, the water-soluble fraction (mainly transition metals with redox potential) has an important role in the initiation of oxidative DNA damage and membrane lipid peroxidation (Costa and Dreher, 1997; Osornio-Vargas et al. 2003).

PM health effect on respiratory system

The respiratory system is the target of the toxic effect of many chemical compounds, biological agents, and foreign particles deriving from environmental pollution. For the anatomic position and the respiratory functions, the respiratory system is continuously in contact with the harmful agents present in the atmosphere. The particulate material tends to settle easily at the level of bifurcation or angle of bronchial tree. Most of the inhaled particles also can be accumulated in the lymph nodes placed in series with the lymphatic vessels that drain the lung, thus involving the immune response.

Lung deposition of airborne dusts appears *in vivo* like small, barely visible blackish dots, identified as carbon particles within macrophages. Moreover, carbon-dust accumulation in lymph nodes appears as an organization of minute, dark spots arranged as a crown between cortex and medulla. These macroscopic and microscopic features are appreciable also in animals farmed nearby industrial areas (Fornero et al. 2009; Perillo et al. 2009).

The adverse effects of ultrafine air particles are linked to their ability to gain access to lung and systemic circulation, where toxic components lead to tissue damage and inflammation. While the particles with greater diameter, due to air flow and turbulence, can penetrate into the upper airways and are normally expelled from the mucociliary clearance, the finest fraction (PM_{2.5}) is deposited in the deeper parenchyma and have access to the alveolar ducts and the alveolus (Shusterman 2011; Falcon-Rodriguez et al., 2016). This fraction can produce cell signaling, expression of inflammatory mediators, and oxidative stress (Deng et al., 2013; Wang et al. 2013; Kelly and Fussell, 2015b).

Once deposited on a particular region in the lung, polluting agents can penetrate or be absorbed by the mucous layer, generating local or systemic damage. Absorption of toxic substances depends on several factors, first of all the physical, chemical, anatomical, and functional properties of the cardio-

respiratory system (Perillo et al. 2009). The respiratory system, in fact, has the ability to protect itself from pathogenic noxae through immunological and non-immune mechanisms, and the reactions and their damaging impact are functions of individual reactivity (Olivieri and Scoditti, 2005). Epidemiologic studies demonstrated that ambient PM and diesel exhaust particles (DEP) exert deleterious effects on human cardiopulmonary health, including exacerbation of pre-existing lung disease and development of respiratory infections (Karakatsani et al. 2012; Huang et al. 2015). Specifically, PM₁₀ or less can exacerbate pulmonary disorders (Barlow et al. 2008), including COPD and asthma, as well as the increase in allergic inflammation. Additionally, environmental pollutants can negatively influence the effectiveness of the immune system response to pathogens. Numerous investigations described a suppression of immune function attributed to the dysregulated cytokine and chemokine production, a loss of migratory potential, or a severe depression in phagocytosis in macrophages and immune cells exposed to DEP (Sawyer et al. 2010). Many researchers have analyzed the detrimental impact of particulates on alveolar macrophage phagocytosis both *in vitro* and *in vivo* animal studies (Hodge et al. 2003; Sawyer et al. 2010; Rylance et al. 2015). The literature demonstrated how carbon or DEP or PM suppresses phagocytosis of bacteria, fungi, and inert particles (Lundborg et al. 2006; Zhou and Kobzik, 2007; Karavitis and Kovacs, 2011). The available data supported the importance of the impair mechanisms of phagocytosis following exposure to these factors. This effect cannot only leave the host susceptible to infection, but also can promote alterations in many other macrophage functions necessary for pathogen clearance and restoration of homeostasis (Mundandhara et al. 2006; Zhou and Kobzik, 2007). The initiation of the inflammatory response, the bronchial hypersecretion, the cellular chemotaxis, and the release of chemical mediators represent both a first defensive reaction and the beginning of the main structural alterations of the lung parenchyma. These are the typical lesions observed in pre-existing chronic respiratory diseases such as obstructive bronchopneumopathy (COPD) and it is well known that long-term exposure to PM could lead to pulmonary diseases such as COPD, asthma, and fibrosis or their exacerbation (Jones and Richeldi, 2014).

PM lung impact: biomolecular pathways and cellular response

Toxicological and *in vitro* studies investigated the biological and molecular mechanisms of action involved in PM-induced injury, inflammation, and lung toxicity (Riva et al. 2011; Wang et al., 2013). Results suggested that PM had several mechanisms of adverse cellular effects, such as cytotoxicity through oxidative stress mechanisms, oxygen-free radical-generating activity, DNA oxidative damage, mutagenicity,

and stimulation of proinflammatory factors (Valavanidis et al., 2008; Cachon et al. 2014). Findings showed the ability of PM to induce oxidative stress and to cause inflammatory cytokines gene expression and secretion (Cachon et al. 2014).

Exposures to air pollution in the form of PM can result in excess production of ROS in the respiratory system, potentially causing both localized cellular injury and triggering a systemic inflammatory response (Sijan et al. 2015). The observations indicated that air pollution particles generate oxidative damage of DNA by promoting a milieu of oxidative stress and inflammation (Pralhad et al. 2001; Møller et al. 2014; Kelly and Fussell, 2015a). Oxidative stress is linked to several DNA lesions and the formation of bulky adducts—mechanisms by which PM could elicit mutagenesis and in turn cause cancer. Data have also demonstrated that air pollution promoted a systemic vascular oxidative stress reaction inducing endothelial dysfunction and monocyte activation (Bind et al. 2012; Bourdrel et al. 2017).

PM-induced inflammation in the lung is modulated in large part by alveolar macrophages (AMs) and their biochemical signaling, including production of inflammatory cytokines, the primary mechanism via which inflammation is initiated and sustained. The AMs are one cell type in the lung directly exposed to particle and upon contact with particles (Huang et al. 2009).

In vitro experiments have demonstrated that PM can produce damage to the whole respiratory apparatus, increasing cellular permeability (Cachon et al. 2014) and reducing the mucociliary activity by ROS production and cytokine releases (Falcon-Rodriguez et al. 2016). The inflammatory mediators can activate different pathways, such as MAP kinases, NF- κ B, and Stat-1, or induce DNA adducts (Falcon-Rodriguez et al. 2016). Many studies confirmed the oxidative effect of PM following the increase in NF- κ B (Nuclear Factor-KappaB) levels, a nuclear factor that can induce the transcription of genes encoding cytokines and interleukins (IL-6, IL-8 and TNF- α) responsible for the on-site recall of neutrophils and subsequent tissue damage (Takizawa et al. 1999; Shukla et al. 2000; Churg et al. 2005).

All these alterations can also mediate obstructive or restrictive respiratory diseases such as asthma, COPD, pulmonary fibrosis, and even cancer. The cellular response to the progressive accumulation of PM is characterized by a perivascular and peribronchial infiltrate mainly composed of neutrophils and macrophages, and associated with a T cell lymphocyte component (CD8+) that confirm the role of PM in the pathogenesis of chronic and obstructive lesions. Investigations on animal populations, reared in areas at high environmental risks, also shown histological evidences of peribronchial lymph-plasmocyte and granulocyte infiltrates as well as peribronchial fibrosis after PM exposure (Perillo et al. 2009).

The carbon particles, which represent a large part of the particulate fraction, are also able to induce the recruitment of immature neutrophils from the bone marrow (Terashima et al. 1997; Tatler and Jenkins, 2012), as shown in vivo intratracheal instillation of PM fractions in rats that increased neutrophil incursion and lavage protein concentrations (Ghio 1999). In healthy humans, the experimental exposure to DEP (Diesel Exhaust Particles) (at 300 μ g/m³/h) increased the percentage of inflammatory cells (neutrophils), B and T lymphocytes, and mast cells in the lungs (Nemmar et al. 2013; Huang et al. 2015).

PM and lung morphopathologic and biomolecular chronic features

Pulmonary retention of PM results in a series of events dominated by the release of inflammatory cells, oxidative product, and chemical mediators (cytokines and chemokines) responsible of morphostructural changes in the bronchiolar and alveolar cells (Ling and van Eeden, 2009). At the bronchiolar level, epithelial lining cells are the first target of the flogosis reactions. Cells with vibratile cilia are particularly exposed and sensitive to disturbing agents and the alterations of these structures induce a reduction in the efficiency of mucociliary clearance (Souza et al. 1998; Ling and van Eeden, 2009), thus support the permanence of inhaled particles, as well as the development of secondary infectious pathologies. The release of the mediators of inflammation, in fact, produces cellular lesions with consequent increase in susceptibility to bacterial, fungal, or viral infections (Karavitis and Kovacs, 2011; Rylance et al. 2015).

The exposure to PM also modulate the alveolar macrophage function through a process mediated by oxygen radicals that altering phagocytic activity against microorganisms and reducing the host's lung defenses to infectious agents (Becker et al. 2005a,b; Lundborg et al. 2006).

Composition of particles has a substantial role in the development of oxidative cellular damage and in inducing of biochemical synthesis of proinflammatory mediators, with particular attention on the presence of transition metals such as vanadium, copper, platinum, manganese, and iron. An experimental study demonstrated that titanium dioxide nanoparticles (TiO₂) rise the number of neutrophils and macrophages recruited in the bronchoalveolar lavage fluid (BALF) (Bermudez et al. 2004). These compounds have a marked ability to promote ROS production and therefore play a role in inducing tissue damage. Exposure to ambient particles could lead to pulmonary fibrosis (Tanjore et al. 2012), especially the exposure to elements or chemicals such as Al, Si, carbon black, TiO₂, silicon oxide, talcum powder, asbestos, and other fibers can cause epithelial damage and rise the levels of IL-2 and IL-8 (Fornero et al. 2009; Szema et al. 2014).

Long-term exposure leads to chronic reactions, thus causing a progressive destruction of the pulmonary parenchyma followed by fibrotic repair processes. The subsequent tissue remodeling is conducted by the macrophages action. Cellular activation inducing the production of free radicals and is associated with the release of lysosomal enzymes (collagenase, elastase) responsible of promoting the interstitial disorganization (Ciencewicki et al., 2008). Furthermore, recruiting cells produces an excess of extracellular matrix components (Wynn 2011) and promotes the pulmonary remodeling like an irreversible distortion of the lung's architecture. In this event, the deposit of collagen fibers is stimulated by TGF- β , a potent mediator of fibrogenesis (Wang et al. 2011; Tatler and Jenkins, 2012).

The tissue lesions involve both the bronchiolar walls and the pulmonary parenchyma with ducts and alveolar sacs. At the alveolar walls, destructive modifications conduce initially to lesions due to oxidative stress like emphysema, apoptosis, and the proteolysis of the pulmonary tissue (Hogg 2006; Mannino et al. 2006). This lesions resulted by the action of the elastases and metal-proteinases (MMPs) released by neutrophils and macrophages (Lim et al. 2000; Montano et al. 2004). Repair and remodeling events, on the other hand, are responsible for a progressive obstruction of airways conduits (Hogg 2004; Hogg et al. 2004; Mannino et al. 2006). Churg et al. (2005) referred that chronic inflammation is associated with tissue proliferation and thickening of the bronchial walls with consequent airflow obstruction. Secondary pulmonary fibrosis (sclerosing alveolitis) is in fact characterized by proliferation of fibroblasts and production of collagen fibers with consequent thickening of the interstitium.

This response also come under macrophages control that release growth factors or fibrogenic cytokines having a mitogenic effect on fibroblasts (PDGF- Plateled Derived Growth Factor, TGF- β -Transforming Growth Factor β , AMDFG-Alveolar Macrophage Derived Growth Factor) (Bonner 2007; Wang et al. 2013). The PM can induce an increasement in the PDGF with NF- κ B is indispensable in survival factors inhibiting cellular apoptosis and promoting proliferation (Romashkova and Makarov, 1999). They also can determine myofibroblast differentiation and production of collagen fibers in the lung (Byrne and Baugh 2008).

Animal populations exposed to pollutants can suffer like humans from the potential acute and chronic effects of such exposure. The literature, although poor for animals, confirms that exposure to dusts may result in persistent inflammation, pulmonary fibrosis, and cellular and tissue remodeling in specific regions of the lung where particles tend to accumulate (Fomero et al. 2009; Perillo et al. 2009).

A morphological study conducted on bovine farmed near-by an industrial area observed the structural alterations that occur after daily exposure to high level of PM airborne concentration (Perillo et al. 2009). Lesions provide further

evidence of the lungs reactive response to toxic substances. The most remarkable aspect of the observations was the fibrotic reactivity at peribronchial, perivascular, alveolo-capillary, and pleural levels. The close association between connective tissue proliferation on the one hand, and macrophages activated by the presence of extraneous particulate material on the others, confirmed both the central role of macrophages in fibrogenetic process modulation and the importance of aerodispersed dusts involved in pathogenesis of chronic pneumopathies.

An increasing understanding of the mediators and the mechanisms of action is necessary in the animal sentinel systems that are designed to the identification or monitoring of environmental contaminants dangerous to the human and to the ecosystem health.

Conclusions

The particulate matter represents a key indicator of air pollution brought into the air by a high variety of natural and human activities. Consistent evidences from both epidemiological and experimental studies have demonstrated that short- and long-term exposure to particulate matter, especially to the finest particles, is associated with cardiopulmonary injury and systemic diffusion. Experimental studies conducted on laboratory animals have shown that the pulmonary inflammatory response following inhalation of airborne dust is characterized by a local increase in macrophages and neutrophils as well as by activation of alveolar macrophages. Activation of monocytes determines the free radicals (ROS) production as well as the release of cytokines playing an important role in the development of fibrotic lesions. The fibrotic process is important for tissue repair, but if the tissue proliferation exceed, it can alter and compromise the structure and physiological functions of lung. Pollutant particles reaching the lung parenchyma via the airway may remain for years, and generally determine pneumopathies and sclerosing pneumoconiosis. In conclusion, a depth knowledge of the health effects of exposure to particulate matter can provide vital information for health impact assessments. More studies on animals reared in areas at high risk of pollution may be helpful to establish the importance of animal sentinel on the process of evaluating risks and to formulate regulatory procedures, as well as the evaluation of the occurrence of the pathological manifestations.

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