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# Effect of Particulate Matter on Human Health, Prevention, and Imaging Using PET or SPECT

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Particulate matter (PM) in dust causes serious pathological conditions, and it has been considered a critical health issue for many years. Respiratory disorders such as bronchitis, asthma, and chronic inflammation, are the most common illnesses due to PM that appears as dust. There is evidence that cardiovascular and neurological abnormalities are caused by PM. Although an extensive amount of work has been conducted on this topic, including studies on the nature of the particles, particle size measurements, particle distribution upon inhalation, the health effects of fine particles, disease prevention, diagnosis, and treatment, to this date, there is still a considerable lack of knowledge in these areas. Therefore, the identification of the key components that cause diseases owing to PM, and the specific diagnoses of the diseases, is important. This review will explore the current literature on the origin and nature of PM and their effects on human health. In addition, it will also highlight the approaches that have been adopted in order to diagnose the effects of PM using positron emission tomography (PET) or single-photon emission computerized tomography (SPECT).

Keywords: Particulate matter, PET, SPECT, Imaging

## Introduction

Air pollution was heterogeneous in nature and arises from the presence of gases, liquids, and particulate matter (PM). In general $PM_{10}$ and $PM_{2.5}$ stood for airborne particles that was smaller than 10 μm and 2.5 μm, respectively, in diameter in the atmospheric field.[1,2] Mainly in health-science community, fine particles and ultra-fine particles was operationally defined as those having diameters less than 2.5 μm and 0.1 μm, respectively.[2] The chemical composition of PM varies depending upon its characteristic properties. Approximately a third of the earth's land surface was covered with arid and semiarid regions, which constitute a major supply source of Aeolian dust. Depending upon the meteorological condition, suspension of crustal particles to the atmosphere was occurred throughout the year. Global dust aerosols with diameters of 10 μm or less correspond to bulk dust strengths in the range of 1000~3000 Tg/yr.[3,4] More than 400~1100 Tg/yr of modern dust aerosols was originated in China. A study conducted in various northwestern regions of China estimated the availability of modern dust aerosols and reported that their emissions were generated owing to the Aeolian process.[4]

The composition of PM varies from place to place and depends considerably on the parent environment. The global average chemical composition of $PM_{2.5}$ was reported

to be sulfate (20%), crustal material (13.4%), equivalent black carbon (11.9%), ammonium nitrate (4.7%), sea salt (2.3%), trace metal oxides (1.0%), water (7.2%) at 35% relative humidity, and residual matter (40%).[5] In a study conducted in 2005, the inspection of the Saharan desert dust was carried out using scanning electron microscopy.[6] The mineralogical phase composition by transmission electron microscopy and aerosol size distribution by optical particle spectrometer were studied and compared. Results revealed that the average composition (by volume) of aerosol was dominated by mineral dust contained 64% silicates, 6% quartz, 5% calcium-rich particles, 14% sulfates, 1% hematite, 1% soot, and 9% of other carbonaceous materials especially for particles larger than 1 μm.[6]

The composition of PM in Asia investigated by the Asian Pacific Regional Characterization Experiment (ACE/Asia) revealed that the primary components of fine particles in mixed mineral dust-pollution plumes were $Mg^{2+}$ and $Ca^{2+}$.[7] Moreover, the composition of roadside dust was dominated by Fe, Cr, and Ni, while particles rich in W and trace elements were also reported, as suggested by a study in Finland using scanning electron microscopy.[4] In modern concrete jungles, the concentration of PM was greatly increased, and its adverse effects on humans were propelled the utter need to design strategies for diagnosis and prevention. Demolition of buildings and concrete structures were considered as one of the major sources of aerosol dust emission.[7,8] A study was conducted in Baltimore (USA) which suggested a great increase in PM after experimentation on three demolition sites.[8,9] In another study in Tokyo, PM samples were collected from streets, and hydrocarbons were analyzed using capillary gas chromatography following HPLC fractionation. The study suggested that PM in metropolitan cities was mainly owing to automobile exhausts and the burning of fuels, while residential areas receive significant amounts of dust from the settling of PM emitted from forest fires, volcanic eruptions, etc..[10] Industries served as major contributors to the particulate matters by releasing gases that contain particles.[11,12] Moreover in a long term project of surface particulate matter network (SPARTAN) various ions, and trace metals were characterized and quantified from worldwide data collection. Details of the contents can be found in the paper by Snider G et al. thus, revealing data on variation in the global PM chemical composition.[5]

## Particulate Matter and Its Impact on Human Health

Pollutants from many different sources were parts of the air we inhale. The type of pollutant varied depending on the geographical distribution, area, workplace, and season. Personnel working in industrial areas was more prone to air pollution. The PM derived from various pollution sources upon inhalation produces serious effects on the skin, arteries, lungs, heart, and eyes.[12-19] The brain was also affected by the PM, depending upon the particulate size and charge.[20] The characteristics of the PM determined the potential biological effects.[21] A group of researchers showed that the size of PM regulated its potential to cause an injury, or oxidative, inflammatory, and other biological responses.[1,21]

Both long- and short-time exposures to PM was of serious concern. Sustained long-time exposure in the environment for many years was linked to serious cardiovascular, respiratory, and skin diseases. Short-time exposure led to morbidity incidents in all ages owing to cardiovascular and respiratory diseases caused by inhalation of airborne dust particles.[22] According to the United Nations environmental program, approximately 1.1 billion people died owing to PM. Inhaled PM can penetrate deeply into the lungs, which constituted a particular concern owing to the serious hazardous effects they cause. There was an evidence that airborne particles was associated with cardiovascular diseases.[23] There was a report that PM was a possible cause of stroke.[24]

Table 1 listed the classification and related pronounced pathological conditions documented thus far. Fig. 1 shows the diagrammatic representation of inhaled PM of variable sizes and imaging of effect of PM on human health using Positron Emission Tomography (PET) or Single-Photon Emission Computerized Tomography (SPECT).

## Effects of Particulate Matter on Heart

Air pollution and its associated cardiac risk, as published

**Table 1.** Scientific classification of particle sizes and related diseases.

| Scientific Nomenclature | PM size (μm) | Exposure | Infected site | Disease | Reference |
|---|---|---|---|---|---|
| Coarse | $PM_{10\sim2.5}$ | 5~10 μg/m$^3$ | Eye | Allergic conjunctivitis | Baldacci S (2015) Jalbert I (2015)[70,71] |
| Coarse | $PM_{10\sim2.5}$ | 2~5 μg/m$^3$ | Nose | Allergic rhinitis, | Jalbert I (2015)[71] |
| Fine | $PM_{2.5\sim0.1}$ | 1~2 μg/m$^3$ | Lungs | Bronchitis, pulmonary emphysema, asthma | Jalbert I (2015)[71] |
| Fine | $PM_{2.5\sim0.1}$ | 0.1~1 μg/m$^3$ | Lungs | Induction of alveolar damage | Jalbert I (2015)[71] |
| Ultrafine | $PM_{<0.1}$ | 0.1 μg/m$^3$ | Brain | Ischemic stroke | Tian Y (2017)[72] |

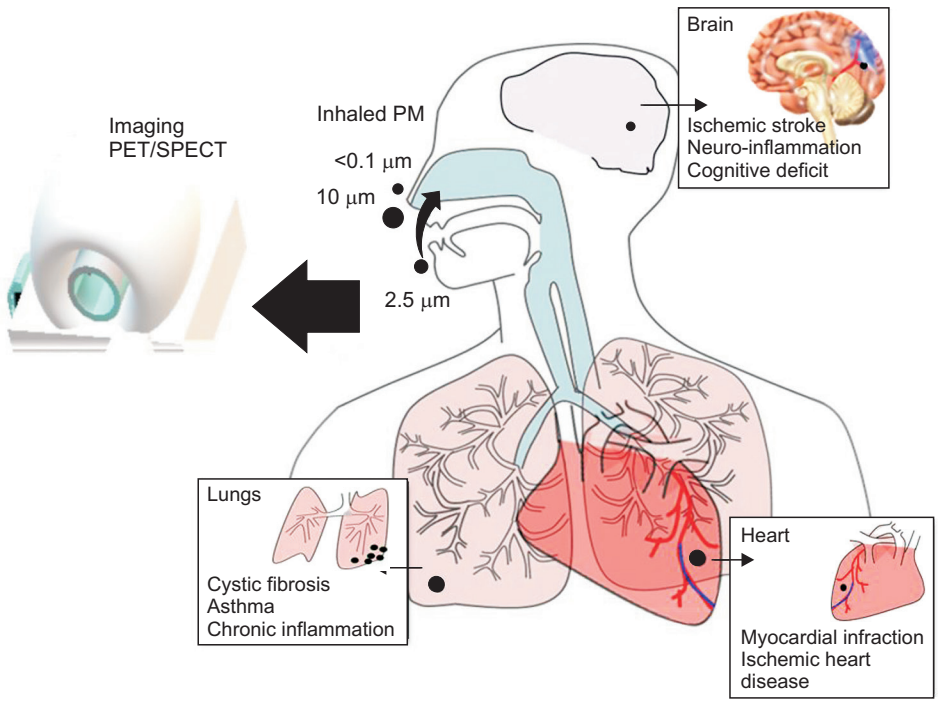


**Fig. 1.** Diagrammatic representation of inhaled particulate matter (PM) of variable sizes. PM-linked respiratory, cardiovascular, and neurological disorders and imaging of effect of PM on human health using PET or SPECT.

by the American Heart Association, underlines the set aim to investigate the harmful cardiovascular effects that arise from the exposure to air pollution. Many researchers reported that particles with diameters of 2.5 μm or less was associated with the elevated risks of cardiovascular events.[23,25] Cardiovascular risk implications that could arise from the changes in the blood composition include the irregularity of the heart rate, and plasma viscosity and blood pressure changes. In addition, increases in PM concentrations was associated with increased chances for myocardial infarction.[23,25]

Epidemiological research was initiated after the increased mortality rates that occurred as a result of the fog in the Meuse valley in December 1930, and following the London smog incident of 1952.[26,27] Studies on the long-term exposure to PM was fewer, and involved the total mortality as well as cardiovascular events. Increased alveolar inflammation occurred as a result of the inhaled particles that further exacerbate any preexisting lung disease, thus causing increased blood coagulation, and ultimately leading to increased cardiac risk factors.[28,29] Middleton et al, analyzed the respiratory and cardiovascular morbidity of short-term exposure of air pollution and dust storms in two hospitals in Nicosia, Cyprus. They reported an increase in hospital admissions for cardiovascular events by 1.2% for every elevation in particle concentration by 10 μg/m$^3$ ($PM_{10}$). Moreover, they concluded that risk of cardiovascular disease increased during dust storm days.[30] Similarly, Pope IC et al. reported statistical analyses of long-term

exposure of PM increased the chance of ischemia, heart failure, and cardiac arrest. A mortality risk in the range of 8% to 18% was linked to increases of $PM_{10}$.[31] Cardiovascular health effects was correlated between carbon content and the change in blood pressure measurements. Following 2 hr exposure to PM, changes in blood pressure were observed.[32,33] Similarly, a case cross-over study of exposure to urban traffic studied the occurrence of myocardial infarction and concluded that the risk of occurrence of this disease may increase in susceptible persons with transient exposure to urban traffic.[34]

In a stratified case cross-over study design, correlation between cardiovascular disease (CVD) and PM effects were found from a database in Wales and England.[29,35] In summary, the morbidity events in reported publications associated with PM include myocardial infarction, stroke, venous thrombosis, initiation of atherosclerosis, dysfunction of the autonomic nervous system, ischemic reposition, and altered ion-channel function in myocardial cells.[36,37]

## Effect of Particulate Matter on Lungs

The direct effects of PM may be attributed to the contact of PM on the epithelium of human lung airways. It was speculated to be the cause of the toxic effect of PM originated from various chemical sources. These sources included the combustion of fossil fuel, power generation, vehicle exhaust, industrial process acid, as well as by various organic compounds, including pathogens, fungi, pollens, and viruses.[38] Using 10-year data from Taiwan's national health insurance research database (NHIRD), Kang et al, conducted a study on the relationship of the Asian dust storm and number of pneumonia admissions in a Taiwan city. The results showed that there was an increased number of admissions to hospitals during the dust storm season.[39-42] The effects of PM on the lungs was evident because the lungs was the first systemic organ to interact with PM via the respiratory system upon inhalation. The PM was cause of numerous diseases, one of which was known as silicosis, manifested by lung fibrosis caused by the inhalation of dust-containing silica. It was reported that it was more dominant in humans working in the industries of sandblasting, flint crushing, the ganister industry, and the manufacturing of abrasive soap. Similarly, inhalation of asbestos causes asbestosis. Both silicosis and asbestosis were incurable and even after exposure ceases, the disease may still progress.[43] The changes of lung function was due to a generalized diffuse fibrosis rather than the nodular fibrosis pattern observed in silicosis. The suggested underlining mechanism was based on the fact that asbestos decomposes in the lung by depositing $SiO_2$ following the removal of metallic oxides of asbestos.[44] Bhattacharjee et al, reviewed the genetic and epigenetic alteration in occupational exposure to silicon asbestos and arsenic.[45] Asthma, a breathing disorder was connected to PM. It was reported that endotoxin, a pro-inflammatory agent present in house dust, may be the cause of asthma. It was demonstrated by a cross-sectional study design on 69 patients who had rhinitis or asthma that the concentration of endotoxin in house dust is a contributing factor in the etiology of asthma.[46] Moreover, chronic obstructive pulmonary disease (COPD) was also associated with PM. Study and research was suggested that upon exposure to $PM_{10}$, PM enhanced the chances of being affected by COPD. It also affected the functioning of lungs in elderly and susceptible patients, as explained by Ming-tai Lin et al, in their investigation to identify the association between acute exacerbation of chronic obstructive pulmonary disease and climatic change.[47] Another respiratory disorder was tuberculosis which constitutes a global challenge. A cross-sectional study conducted on slate pencil workers and quartz stone crushers who were highly exposed to silica dust showed that the tendency of being affected by tuberculosis was greater compared to people who lived in clean environments.[48] Bronchitis, the inflammation of the bronchial tubes was another malady connected to dust. The PM have been found to cause inflammation of the airway that causes bronchitis. It was more commonly found in people exposed to PM, such as in dryland farming areas.[49]

## Effect of Particulate Matter on Brain

Although the blood brain barrier effectively protects the brain, this may not always be the case. Thus, this secure barrier may not be safe and does not entirely protect the brain from PM. It was evident that pollution directly af-

fects human health in accordance to recent studies that have found and reported various toxic effects, including cardiovascular, respiratory, and neurological toxicities. $PM_{2.5}$ can cross the blood brain barrier. The effects of PM sizes on the brain were first reported in 1998 by conducting a cohort study that comprised 957 patients exposed to indoor coal fumes in Shanghai. The study indicated that the individuals who were exposed to coal fumes yielded an increase incidence in ischemic stroke that is the leading cause of death in the Shanghai.[50,51] Recent studies indicated that PM could attack the brain parenchyma causing neurodegenerative disease. Alzheimer's disease (AD) and Parkinson's disease (PD) are neurodegenerative diseases and affect a significant number of humans all over the world. To identify the correlation between PM and neurodegenerative disease, a prior study was carried out on canine naturally exposed to PM. The study concluded that a significant increase in DNA damage (apurinic/apyrimidinic sites) in olfactory bulbs, frontal cortex, and hippocampus, were observed when dogs were exposed to PM. According to the study, the nasal pathways was known the point of entry for PM. Another study performed on human and animal models suggested that brain exposed to PM led to increases in CD-68, CD-163, and HLA-DR positive cells. Also noted, there were elevated pro-inflammatory markers interleukin-1b, cyclooxygenase 2, increased Ab42 deposition (hallmark disease protein of Alzheimer's disease), BBB damage, endothelial cell activation, and brain lesions in the prefrontal lobe. Furthermore, these studies suggested that PM caused cytokine production, increases in MAP kinase, neurochemical changes, lipid peroxidation, enhanced NF-kb expression, and behavioral changes. Exposure to PM not only causes neuro-inflammation but also the accumulation of beta amyloids which was considered to be the cause of AD. Additionally, it leads to increases in $\alpha$-synclines which are the components of Lewis bodies, and which was speculated to cause PD. It was found that their accumulation starts in childhood when the body was exposed to PM. Eventually, this causes premature aging in the brain, and initiates the development of disease as a result of the alteration of the aggregation and rate of protein fibrillation by nanoparticles. MRI analyses of brain images acquired from children exposed to PM revealed structural damages localized to the prefrontal cortex.[51-53]

Because the majority of the world population resides in urban areas, and was prone to PM, the problem of the increase prevalence of CNS diseases would be important and needs to be investigated. Increases in stroke hospitalizations were observed with PM as Yang et al and Kang et al, described while working in Taiwan.[54,55] Table 2 listed the studies that were conducted to evaluate the effects of PM on vital organs.

## Imaging of the Effects of Particulate Matter

After inhalation of PM, assessment of their bio distribution would be important in terms of risk management. Many factors was responsible for the PM deposition and diffusion in the body after inhalation. Nevertheless, limited data was available on the clinical diagnostic strategy of PM. Imaging the effects of PM could be conducted using planar scintigraphy, SPECT and PET.

### 1. Gamma scintigraphy or SPECT

Gamma scintigraphy was a conventional method used in nuclear medicine for diagnostic purposes.[56] The limitation of gamma scintigraphy was the 2D image, and the measurement of the distribution of aerosol deposition was limited owing to the lack of spatial resolution. Laube et al., used gamma scintigraphy to measure the targeted aerosolized medication in peripheral airways in cystic fibrosis patients, and found that PM deposition can be achieved by varying the particle size and inspiratory flow rate.[57] To determine the particle deposition and clearance, the imaging of radio-aerosoles with gamma cameras was a well-established technique. SPECT imaging was based on the use of gamma cameras to provide three-dimensional images. The radioisotopes used with tracer in SPECT imaging are $^{123}I$, $^{99m}Tc$, $^{133}Xe$, $^{201}Tl$, $^{67}Ga$ and $^{18}F$. Whereas among radioisotopes, $^{99m}Tc$ was most commonly used tracer.[58] Inhaled PM could be traced using $^{99m}Tc$-labelled PM. Nemmar et al.'s study showed that $^{99m}Tc$-labelled particles were deposited in the body organ and thus detected over thyroid, salivary glands, liver, bladder and stomach.[59]

**Table 2.** List of prior conducted studies explaining the effects of PM on systemic organs.

| Year | Title | Reference |
|---|---|---|
| Cardiovascular | | |
| 2018 | The association between exposure to air pollutants including $PM_{10}$, $PM_{2.5}$, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide concentrations, and the relative risk of developing STEMI: A case-crossover design | Akbarzadeh et al.[73] |
| 2014 | A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effects of short-term changes in air pollution and dust storms | Middleton et al.[30] |
| 2012 | Effect of dust storm events on daily emergency admissions for cardiovascular diseases | Tam et al.[37] |
| 2008 | Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions, and mortality | Milojevic et al.[29] |
| 2005 | Acute blood pressure responses in healthy adults during controlled air pollution exposures. Environmental health perspectives | Urch et al.[32] |
| 2004 | Exposure to traffic and the onset of myocardial infarction | Peters et al.[34] |
| 2003 | Air pollution and hospital admissions for ischemic heart diseases among individuals who are 64+ years of age residing in Seoul, Korea | Lee et al.[36] |
| 2002 | Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults | Brook et al.[33] |
| Respiratory | | |
| 2000 | Targeting aerosol deposition in patients with cystic fibrosis | Laube et al.[57] |
| 2001 | Air pollution and hospital admissions for respiratory conditions in Rome, Italy | Fusco et al.[42] |
| 2007 | Tuberculosis among workers exposed to free silica dust | Tiwari et al.[48] |
| 2008 | A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effects of short-term changes in air pollution and dust storms | Middleton et al.[49] |
| 2011 | Quartz exposure and increased respiratory symptoms among coal mine workers in Tanzania | Mamuya et al.[16] |
| 2012 | Potential determinants of coal workers' pneumoconiosis, advanced pneumoconiosis, and progressive massive fibrosis among underground coal miners in the United States | Laney et al.[15] |
| 2016 | Risk of occupational exposure to asbestos, silicon, and arsenic, on pulmonary disorders: understanding the genetic-epigenetic interplay and future prospects | Bhattacharjee et al.[45] |
| 2018 | Effects of particulate matter on allergic respiratory diseases | Wu et al.[21] |
| Neurology | | |
| 2005 | Effects of Asian dust storm events on daily stroke admissions in Taipei, Taiwan | Yang et al.[54] |
| 2008 | Air pollution, cognitive deficits, and brain abnormalities: A pilot study with children and dogs | Calderón-Garcidueñas et al.[52] |
| 2009 | Air pollution: mechanisms of neuroinflammation and CNS disease | Block[51] |
| 2013 | Asian dust storm events are associated with an acute increase in stroke hospitalisation | Kang et al.[55] |
| 2018 | Air pollution and stroke | Lee et al.[53] |

## 2. PET

PET imaging was a noninvasive nuclear imaging test that uses radionuclides as tracers, the drugs that was used in PET studies of aerosols are $^{11}$C-triamcinolone, $^{11}$C-formoterol, $^{18}$F-insulin, $^{124}$I-insulin, and $^{125}$I-insulin.[60-63] $^{18}$F-FDG was the most commonly used tracer for the study of lung physiology. PET scans was mostly used to diagnose disease at the cellular level given that disease begins at this level. PET data could provide better diagnostic accuracy compared to SPECT.[64,65] Because most of the inflammatory cells metabolize glucose as a source of energy, FDG PET could besed to detect and diagnose many diseases and inflammations. The prime feature of FDG PET lies in its applications, whereby it can identify diseases or inflammations in their early stages, thus providing advantages in its theranostic applications. Therefore, conventional FDG PET could be used to diagnose the inflammation caused by PM. Its use can detect the inflammation in its early stages and because it can be treated immediately after detection.[66]

## Rescue the Effects of Particulate Matter

The inhalation of PM led to inflammatory lung diseases and asthma, and consequently elicits a systemic disease manifestation, such as osteoporosis and fracture. Systematic bone loss was a major health problem and utmost attention was required to deal with this malady. Bone loss has been a linked feature with air inflammatory diseases, yet there was no strategies designed to cease their progression. Vitamin D was essential for bones, and its deficiency causes bone loss and hyperparathyroidism. Experiments were designed to discover whether the supplementation of Vitamin D could help prevent systematic bone loss. Mice were subjected to high/low Vitamin D supplementation for five weeks followed by their exposure to ordinary dust extracts (ODE) or lipopolysaccharides (LPS) for three weeks. The results obtained showed no differences between the extent of ODE and LPS induced by inflammatory cell infiltration, or by the histopathology of the lungs in the cases of high/low vitamin D treatments. Using micro-CT analysis, it has been shown that increased vitamin D supplementation helped recover the loss of bone mineral density, bone volume, and the weakening of the bone's micro-architecture. With the treatment of vitamin D, bone-reabsorbing osteoclasts decreased as well. However, reduced Vitamin D supplementation did not accomplish any of the results that were accomplish using increased Vitamin D supplementation. Thus, increased concentrations of Vitamin D proved successful for the protection against systematic bone loss but did not succeed in preventing and providing protection against airway inflammation caused by ODE or LPS.[67] Another attempt expended in formulating a preventive therapeutic strategy to overcome the effects of PM indicated that PM originated from concentrated animal feeding operations (CAFO's). CAFO's caused airway inflammatory diseases in exposed workers. Omega-3 fatty acids were found to attenuate inflammatory processes. A pilot research study was conducted to identify whether it could reduce the airway inflammation caused by organic dust. Human body cells were pretreated with omega-3 fatty acid docosahexaenoic acid (DHA), and were then subjected to dust from CAFO's (ODE), and were reported to reduce ODE-induced inflammatory cytokine production. Moreover, mice were treated with DHA for seven days before they were subjected to ODE. The results were compared with mice that were subjected to ODE alone, and it was found that mice treated with DHA showed major reductions in neutrophil infiltration and pro-inflammatory cytokine/chemokine production in ODE-induced bronchial alveolar lavage. It was suggested that the DHA served to reduced airway inflammatory diseases. Hence, DHA supplementation may be an effective way to reduce air inflammatory diseases caused by PM.[68]

## Discussion

PM varies in composition, size, and nature, depending upon the metrological condition. The effects of these PM have become a major issue during the past few years, especially in Asia. Although extensive research has been conducted on the emergence of health issues linked to PM, to-this-date, there was still limited available data describing the specific PM-related health issues.

It is of extreme importance to not only identify the toxic chemical compound in the atmosphere but to quantify its uptake in biological models in order to predict and evaluate the associated potential risk. Inhalation of polyhexamethylene guanidine was quantified using radio-isotope labelled method on nuclear imaging system by Jeon et al.[69]. These radiolabeling technique would be useful for imaging PM.

Imaging was significant in understanding, diagnosis, and treatment of various diseases, ailments, and inflammations. Undoubtedly, imaging has been one of the most important scientific tools of the twenty first century. Nuclear medicine imaging technique such as PET or SPECT could provide the information of bio distribution of PM, and their effects on human.

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## Conflicts of Interest

The authors have nothing to disclose.

## Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

## Ethics Approval and Consent to Participate

The study was approved by the institutional review board (IRB approval number; 2018-0016).

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