Health Effects of Ultrafine Particles (PM$_{1.0}$): A Review

Shaurya Johari*, Ishant Goel†, Anubha Mandal‡

Abstract

Particulate Matter, also known as aerosols, is suspended solid and liquid particles in the atmosphere. These particles are of different sizes and ranges from 0.001-100 µm. It is composed of inorganic elements, ions (like sulfates, nitrates etc.), poly-aromatic hydrocarbons, elemental carbon and some other organic constituents. The major man made sources are vehicular, industrial, coal and biomass emissions. In the recent years, the concentration of particulate matter has increased exponentially. PM has shown major health effects like respiratory and cardiovascular diseases. Apart from PM$_{2.5}$ and PM$_{10}$, which are being given major attention, PM$_{1.0}$ has now become a matter of concern. Our study concentrates on the reason that why the research on Ultrafine particles (PM$_{1.0}$) is of greater importance. These particles can stay in the atmosphere for days or weeks and thus can be transported over long distances in the atmosphere and are highly potent than the coarser particles as their size is 10 times smaller than PM$_{1.0}$. Various health effects are associated with these particles like lung and heart diseases, increased risk of death, impaired pulmonary function etc. Thus a need for consideration of PM$_{1.0}$ as a major pollutant is generated and its adverse impacts should be taken into account to apply the separate mitigation measures for PM$_{1.0}$.

Keywords: Ultrafine particles, Health, Effects, Oxidative stress, Inflammatory.

Introduction

Air pollution is a major concern not only in metro cities but also in other developing cities. Pollutants like CO$_2$, SO$_2$, NO$_x$ Suspended particulate matter (SPM), respirable suspended particulate matter (RSPM) etc. have a direct impact on human beings. In developing countries like India, where the industrial boom has led to setting up large scale industries, there is a need to check the pollution level caused by these industries for sustainable development. These pollutants are responsible for a variety of respiratory illnesses (such as asthma, bronchitis), cardiovascular diseases and can cause cancer in humans if exposed for a long period of time. Particulate matter is one of the major pollutants of air pollution. In this, ultrafine particles of aerodynamic diameter <1 µm have become a matter of concern as they can penetrate the respiratory tract more easily other suspended particles due to their fine size [1]. Its major sources are On-road motor vehicles, construction and combustion industries. These particles also have various health effects like DNA damage, cancer, asthmatic problems, cell death, heart problems etc.

Ultrafine Particles and its Sources

Particles that are <1 µm in diameter are commonly defined as the ultrafine particles.

*Student, Department of Environmental Engineering, Delhi Technological University, Delhi, India.
†Professor, Department of Environmental Engineering, Delhi Technological University, Delhi, India.
‡Correspondence to: Mr. Ishant Goel, Department of Environmental Engineering, Delhi Technological University, Delhi, India. Email Id: ishant.dce94@gmail.com

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Generally, the chemical constituents of particulate matter are sulfates, nitrates, ammonium, other inorganic ions such as Na\(^+\), K\(^+\), Ca\(^{2+}\), Mg\(^{2+}\) and Cl\(^-\). Organic and elemental carbon, crustal material, particle-bound water and heavy metals. The most common used size fractions of PM are TSP, PM\(_{10}\), PM\(_{2.5}\) and Ultrafine particles (PM\(_1\)). Typical urban PM\(_{10}\) is comprised of up to 50% by mass of combustion derived, ultrafine carbon centered particles with associated metals including transition metal. Other major components include ammonium salts of nitrogen, Sulphur and chlorine plus geological dust and organic matter\(^2\). Thus, these ultrafine particles among all the suspended particles penetrate into the lungs and get deposited. Hence, they are of greater concern than those particles which are not able to get into the respiratory system.

![Figure 1. Possible Sources of UFP](image)

### Table 1. Properties of Ultrafine Particles

<table>
<thead>
<tr>
<th>Physical</th>
<th>Chemical</th>
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</thead>
<tbody>
<tr>
<td>Number Concentration</td>
<td>Elemental Composition</td>
</tr>
<tr>
<td>Number size distribution</td>
<td>Inorganic ions</td>
</tr>
<tr>
<td>Mass concentration</td>
<td>Carbonaceous compounds (Organic elemental carbon)</td>
</tr>
<tr>
<td>Mass size</td>
<td></td>
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</tbody>
</table>

Shape and electrical charge in culture exposed to fine and ultrafine carbon black particles showed depletion of GSH, a key oxidant in the case of ultrafine carbon black. Rat instilled with carbon black showed great inflammation and depletion of GSH in the lung lavage fluid. Instillation of ultrafine particles into the rat lung with anti-oxidant nacystelin reduced the inflammation by up to 60% compared to rats \([6-8]\).

All these studies show that the ultrafine fine particles cause more inflammation than the coarser particles. This is the central reason for studying its health effects. The ultrafine particles can cause Lungs injury, asthma, cardiovascular diseases, DNA damage, cognitive dysfunction, apoptosis (cell death) and also cancer.

### PM\(_{10}\) and Ultrafine Particles

Some components of PM\(_{10}\) are not very toxic like sulfates, nitrates, chlorides, ammonium and wind-blown crystal dust \([3]\). A number of the components of PM\(_{10}\) have been hypothesized to derive the toxicological effects, one such component being the ultrafine particles \([1]\). However, transition metals and endotoxin are also potential mediators of adverse health effects of PM\(_{10}\). Mainly, ultrafine particles cause more inflammation than the PM\(_{10}\) \([2, 3]\). Also, ultrafine particles have large surface area and
particle number per unit mass. PM$_{10}$ being large in diameter are deposited in the nose or oral pharynx and cannot penetrate to tissues distal to larynx while ultrafine particles can trapped relatively efficiently in the upper airways by diffusion i.e. by Brownian deposition [4]. These particles, due to penetration in the upper airways, are available to be deposited in the bronchial region the deeper lying airways. So, the UFP can easily deposit in the alveolar region.

### Effects of Ultrafine Particles on Health

Earlier it was thought that particulate matter (PM$_{10}$) had no toxic effect as it would be retained by the nose hair. But now studies have shown that the ultrafine particles present in PM$_{10}$ can penetrate the larynx and enter the respiratory tract. The ultrafine particle causes pro-inflammatory responses [5]. According to a study, epithelial cells

![Figure 2](image)

**Figure 2.** Inflammation caused by an equal instilled mass (125 μg) of particles with 50% cut-off aerodynamic diameter of 10 μm (PM10), carbon black (CB) or ultrafine carbon black.

**Table 2 Effects of Ultrafine Particles on Health due to Short-term and Long-term Exposure**

<table>
<thead>
<tr>
<th>Effects related to short-term exposure</th>
<th>Effects related to long-term exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung inflammatory reactions</td>
<td>Increase in respiratory symptoms</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Reduction in lung function in children</td>
</tr>
<tr>
<td>Adverse effects on the cardiovascular system</td>
<td>Increase in chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Increase in medication usage</td>
<td>Reduction in lung function in adults</td>
</tr>
<tr>
<td>Increase in hospital admissions</td>
<td>Reduction in life expectancy, owing mainly to cardiopulmonary mortality and probably to lung cancer</td>
</tr>
<tr>
<td>Increase in mortality</td>
<td></td>
</tr>
</tbody>
</table>

W. MacNee and K. donaldson has proposed a hypothesis for the mechanism of adverse health effects of the ultrafine particles. According to this ultrafine hypothesis, these ultrafine particles are responsible for the creation of reactive oxygen species. Due to this oxidative stress is created. The body creates an inflammatory response to this oxidative stress. Inflammation is a vital response of the body against harmful stimuli, in this case ROS. But excess of inflammation can have a negative effect on the body. The hypothesis is described below:
Generation of Reactive Oxygen Species (ROS)

Reactive oxygen species are hyper active oxygen species which try to attain stability by accepting electrons from its environment. ROS constitute of oxidative species like superoxide anion (O₂⁻), hydroxyl radical (OH), hydrogen peroxide (H₂O₂) singlet oxygen (¹O₂), and hypochlorous acid (HOCL). ROS can be endogenous as well as exogenous. The endogenous ROS is produced intracellularly through multiple mechanisms majorly by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complexes in cell membranes, mitochondria, peroxisomes, and endoplasmic reticulum for different roles like metabolism of oxygen ,cell signaling and homeostasis [9]. The exogenous ROS is produced by pollutants, tobacco, smoke, drugs, xenobiotics or radiations. The ultrafine particle aggravates the ROS level. The primary ROS i.e. superoxide anion is highly reactive and can even rip of an electron from the nucleus of any nearby cell. To counteract these aggravated ROS, the body induces an oxidative stress [10].

The ultrafine particles have a large surface area. As a result, the transition metals get attached to it. These transition metals can also aggravate the ROS levels and can cause oxidative stress [4]. Recent analysis has reported water soluble species including calcium, sodium, ammonium ions, nitrate and sulphate in the ultrafine particles. Other substance like copper, iron, zinc, potassium, chromium and strontium in the ultrafine particle range [11]. Metal like chromium has carcinogenic potential. These metals attached to the ultrafine particles are toxic and can also cause lung, heart and tissue damage.

The electron transport chain, located in the inner mitochondrial membrane for ATP production, is the major source of reactive oxygen species in animal cell [5]. If extreme toxic level of oxidative stress is created by these ultrafine particles, it may result in mitochondrial membrane damage and electron chain dysfunction leading to cell death. If too much damage is present in mitochondria, the cell undergoes apoptosis. Bcl-2 proteins are layered on the surface of the mitochondria, on detection of damage; activate a class of proteins called Bax, which punch holes in the mitochondrial membrane, causing cytochrome C to leak out. This cytochrome C binds to apoptotic protease activating factor-1 (apaf-1), which is free-floating in the cell’s cytoplasm. Using energy from the ATPs, the Apaf-1 and cytochrome C bind together to form apoptosomes. The apoptosomes bind to and activate caspase-9, another free-floating protein. The caspase-9 then cleaves the proteins of the mitochondrial membrane, causing it to break down and start a chain reaction of protein denaturation and eventually phagocytosis of the cell. Thus the aggravated ROS can destroy the energy making unit, the mitochondria [12, 13].

Oxidative Stress

Excess of ROS can have potentially damaging biological responses resulting in oxidative stress phenomenon. Oxidative stress is created when here is an imbalance between the production of ROS and biological system’s ability to detoxify the reactive intermediates or repair the resulting damage. Thus, to overcome the excess ROS, cells can activate enzymatic and non-enzymatic antioxidant systems [14]. This results in activation of oxidative stress responsive transcriptional factors like AP-1 and NF-κB. The imbalance created by the ROS leads to acetylation of the histones which are attached to the DNA. This loses the contact between histone and DNA and exposes the promoter region of the DNA. The transcription factor gains access to the nucleus. As a result, translated proteins or antioxidants such as cytokines and superoxide dismutase (SOD), catalase are formed [1]. The superoxide dismutase (SOD) dismutates superoxide anion into oxygen and hydrogen peroxide. Hydrogen Peroxide is less reactive than superoxide anion and hence exists for a long time and can be dangerous. To counter this, glutathione catalyzes hydrogen peroxide to form
glutathione disulphide [15]. The reaction is as follows:

\[ 2\text{GSH} + \text{H}_2\text{O}_2 \rightarrow \text{GS-SG} + 2\text{H}_2\text{O} \]

Where GSH is glutathione and GS-SG is glutathione disulphide. Some of the key factors favoring the pro oxidant effects of these ultrafine particles include either the depletion of antioxidants or the increased production of ROS. Disturbance of the normal redox state leads to peroxide and free radical production that has adverse effects on cell components including proteins, lipids, and DNA [14]. Due to its chemical reactivity, oxidative stress can cause DNA damage, lipid peroxidation and activation of signaling networks associated with loss of cell growth, fibrosis and carcinogenesis [16, 17].

**Inflammatory Response**

Basically, inflammation occurs to restore the redox balance by removing the original source causing oxidative stress. Oxidative stress is considered to be a fundamental factor in the generation of inflammation through redox sensitive transcription factors, such as nuclear factor kappa B (NF-κB); the role of NF-κB and oxidative stress in inflammation in general is to create antioxidants that can neutralize the effect of reactive oxygen species. These oxidants burden can exacerbate the condition in case of chronic obstructive pulmonary disease (COPD). This is because the generation of oxidative stress in the airspaces on exposure to ultrafine particles could enhance the already increased oxidant burden which occurs in the lungs of patients with COPD [18]. During exacerbations of the disease there is evidence of systemic oxidative stress, as measured by high release of ROS from peripheral blood leukocytes and a decrease in plasma antioxidant capacity.

Macnee and Donaldson have studied the role of oxidative stress in inflammation. According to their study, Instillation of PM\textsubscript{10} collected in central Edinburgh into the rat lung produces considerably more inflammation (Fig. 2), as measured by Broncho-alveolar lavage neutrophils, than an equal mass of fine (260 nm diameter) carbon particles, this is accompanied by a fall in Broncho-alveolar lavage levels of reduced glutathione and an increase in oxidized glutathione [7]. Generation of oxidants by ultrafine particles has been shown in the studies where free-radicals generated by these ultrafine particles can be quantified by their ability to cause injury to supercoiled plasmid deoxyribonucleic acid (DNA) [19]. Ultrafine particles causes translocation of NF-κB from the cytoplasm to the nucleus in lung epithelial cells in vitro as demonstrated by a fluorescent antibody to the p50 component of NF-κB [20].
Effect on Phagocytosis

Phagocytosis is a process in which a phagocyte digests solids such as bacteria, pathogens etc. that enters the body externally. Phagocytes are a type of white blood cells. The phagocytes engulf the foreign particle and form a vesicle known as phagosomes. It is a part of inflammation where phagocytes are recruited to destroy the external invader. Phagocytes are of two types: microphages and macrophages. The microphages are cells that are mobile in nature and the macrophages are cells which are stationary. Microphages are large in number and are constantly circulating through blood and are also short lived. Whereas macrophages are less in number but they live longer than the microphages. Macrophages are stationed at strategic locations throughout the body. These areas include the alveoli of the lungs, the abdominal and chest cavities, under the top layer of the skin and the intestines.

Mechanism of Phagocytosis

After the detection of the site of infection, the phagocyte cells reaches to the site. The phagocytes activates to macrophages by the presence of chemotaxins. The macrophage attracts the invader through chemotaxis. The macrophage cell gets attached to the foreign material. After attachment, the plasma membrane of phagocyte extends short projection called pseudopods which engulf the foreign materials. After the engulfment, phagosomes come in the contact of lysosomes that contain digestive enzymes and bactericidal chemicals. After making contact the membrane of phagosomes and lysosomes gets fused and a single layered large structure is formed which is called phagosome. Within 10 to 30 minutes, the phagosomes degrade the foreign particle [21].

![Figure 4.Process of Phagocytosis](image)

Donaldson, Stone, PTRS

Phagocytosis by alveolar macrophages is important in the clearance of particle from the lungs. Since the ultrafine particles are large in number, they get deposited into the respiratory tract making it difficult for the macrophage to perform phagocytosis. Thus, they are not readily phagocytized [22].

Effect on Respiratory System

The ultrafine particles are low toxic material but the due to their size they get deposited in large amount. This will primarily lead to strong inflammation response which will damage the lungs. This kind of inflammatory response can exacerbate the condition of compromised persons (in case of COPD). It can lead to
asthmatic attacks, breathing issues, bronchitis etc. If we look at a long term perspective, this can become chronic and thus the respiratory system will become sensitive to ultrafine particles. Another impact due to their deposition is that they won’t get phagocytized by the alveolar macrophage easily. Some studies suggest that the transition metals get attached to the surface of ultrafine particle and as a result can trigger numerous reactions if stayed long enough. The ultrafine particles could also penetrate the lung walls and flow directly into the blood stream. This will create a threat to different organs like heart, liver, intestine etc. Regular exposure to such fine particle can also lead to lung cancer. Another aspect of ultrafine particles is that they get accumulated inside the lungs which lead to chronic inflammation. This chronic inflammation causes mutation of epithelial cells and thus leading to tumor formation in lungs [3, 4, 16].

Effect on Signaling Pathway

The ultrafine particles are said to affect the signaling pathway. Though investigation is still going on and the effect is not understood. According to the hypothesis, the ultrafine particles are said to have transition metal attached to its surface [4]. Calcium signaling is a type of cell signaling in which calcium is utilized for communication governing the activities of the cells. At the neuromuscular junction, the signal is transferred by the neuron to the muscle. In this communication process, calcium plays an important role. The calcium concentration in the endoplasmic reticulum and the cytoplasm is fixed. When the calcium attached to the ultrafine particles comes into the system, it disturbs the concentration of calcium inside the cell and hence hindering in communication process. This can lead to cognitive dysfunction. Regular interference in the signaling process can disturb different body functions and can also cause memory loss in adverse cases.

Effect on Cardiovascular System

The effect of inflammation due to ultrafine particle in the lungs is more understood than the effect of ultrafine particles on cardiovascular system. The inflammation caused by the ultrafine particles is responsible for alteration of blood coagulability and alteration in cardiac electrical activity which cause exacerbation of cardiovascular diseases. It was hypothesized that airway inflammation may activate endothelium and circulating leukocytes, and induce a systemic acute phase response with transient hypercoagulability [26]. MacNee and Donaldson reviewed the issue and concluded that preliminary data in vitro and in vivo suggest that oxidative stress occur in response to ultrafine particles and that the effects of such oxidative stress on changes in blood coagulation may result in the adverse effects of particulate air pollution on the cardiovascular system [27]. Deposition of particles can also hinder the exchange of oxygen and carbon dioxide at alveoli junction and hence stressing the cardiovascular muscles. Cytokines, including tumor necrosis factor and interleukins, have been linked to cardiac arrhythmias and increased levels of platelet-activating factor, a clotting factor implicated in atherosclerosis and cardiac thrombosis. The principal objection to the cytokine hypothesis as applied to cardiac and circulatory effects is the short half-lives of cytokines in the blood [28].
Lipid Peroxidation

Excess formation of ROS can also lead to oxidative degradation of lipids. Lipids are a group of molecules that include fats, monoglycerides, phospholipids and others. The main function of lipids is storing energy, signaling, giving structure to cell membranes. Lipid peroxidation leads to cell damage. It further forms 4-Hydroxynonenal which hinders signaling [29].

DNA Damage

The productions of ROS can also affects the DNA by base modification, a basic sites, non-conventional single-strand breaks, protein-DNA adducts, and intra/inter-strand DNA crosslinks [30]. It is observed that endogenous ROS can modify up to 20,000 bases of DNA per day in a single cell. This can lead to mutation of DNA. Thus, ROS plays an important role in DNA mutation and DNA damage [31].

Conclusion

Thus, we can conclude from this review that the research for ultrafine particles is of great importance. This is because of following reasons:

- Ultrafine particles have larger surface area, number and more probability to penetrate the respiratory tract. Hence it is more potent than coarser particles.
- Ultrafine particles have low toxicity but since their concentration is high, they are much more harmful.
- Ultrafine particles created oxidative stress and inflammation in large amount. Due to this high amount it has health effects on lungs (asthma, bronchitis, breathing problems), cardiovascular system, mitochondria in the cells, cell signaling pathway, and DNA damage.
- Ultrafine particles are everywhere and are in high concentration. Therefore, we are regularly exposed to such kind of particles. Thus, it calls for a need of more research to better understand its health impacts on humans.
- A need is felt to introduce a standard for ultrafine particles so that the industries that are the major source of emission of such potent pollutants should be kept under control.

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