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ULTRAFINE PARTICLES (UFP) AND HEALTH EFFECTS. DANGEROUS. LIKE NO OTHER PM? REVIEW AND ANALYSIS

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ABSTRACT
The goal of the current review is to present and analyze the known information proposed and discussed the last few years about UFP and their possible health effects. It includes references from 1992 to 2008. It also includes references from some fundamental studies in the 1970's and 1980's. The review and analysis of the health hazards induced by ultrafine particle exposure focuses on the; classification and characteristics of suspended particulate matter (PM), features and properties of PM and, specifically, ultrafine particles (UFP), the UFP movement and translocation from exposure sources in the environment to the human body and the ways of absorption and deposition within the human anatomy. Also, an extensive review of epidemiological, clinical and toxicology studies concerning possible health effects of UFP, is included. Finally, the most recent studies suggesting extrapulmonary effects and, especially, on the brain and central nervous system. Results have shown that there is significant analogy between UFP exposure and related adverse health effect risk in human beings. Cardiovascular and pulmonary systems seem to be the main targets of this exposure. New evidence shows accumulation of UFP in regions of the cerebellum, olfactory bulb and other areas of the central nervous system.

KEYWORDS: Air pollution, Ultrafine particles, Nanoparticles, Health effects, Cardiovascular system, Respiratoty system, Central Nervous System

1. INTRODUCTION

Particles in the atmosphere arise from natural sources, such as windborne dust, seaspray, and volcanoes, and from anthropogenic activities, such as combustion of fuels (Diapouli *et al.*, 2008; Guo *et al.*, 2008; Koi *et al.*, 2008; Koulouri *et al.*, 2008; Maraziotis *et al.*, 2008; Polymeneas and Pilinis, 2008; Yang *et al.*, 2008). Suspended particulate matter is technically defined as a suspension of fine solid or liquid particles in a gas condition (Seinfeld and Pandis, 2006). They decrease visibility (main source of haze) and stain the clothes. The ultrafine particulate matter can be breathed, led to and remained in pulmonary tissue, leading to enhanced probability of pulmonary disease and ultimately, lung damage.

Particulate matter is mainly classified by size and their division is as follows (Morawska *et al.*, 2004): *Coarse Particles (CP)* include all particles that their aerodynamic diameter[1] is greater than 2.5 micrometers and less than 10 micrometers. *Fine Particles (FP)* include all particles that their aerodynamic diameter is less than 2.5 micrometers and greater than 0.1 micrometers. *Ultrafine Particles (UFP)* include all particles that their aerodynamic diameter is less than 0.1 micrometers.

[1] *Aerodynamic diameter:* Is the diameter of a sphere with unit density and its mass is equal to the mass of the provided particle.

2. EXPOSURE ROUTES

The main exposure route to ultrafine particles is through the respiratory system, that is, inhalation. When these particles are suspended in the air, there is an increased probability of inhaling them. How deep in the respiratory tree these particles can reach, how long they settle in and what they do when they deposit depends on their size, shape and the particulate matter density. What happens when they deposit in the respiratory system depends on the chemical and toxic properties of the matter (its composition). The particles can even cause problems when consumed as food components, such as coloring and anti-caking agents. These particles deposit in the lung cavity for a few months (WHO, 1997). Finally, one of the most dangerous UFP exposures occurs through smoking, since that helps transfer of dense quantities deep in the lung cavity.

2.1. Absorption and Distribution

UFP absorption seems to primarily happen through the lung, even though particle deposition can be observed anywhere in the body. The initial interaction of these particles with the lung epithelium causes several adverse effects and is mostly responsible for the observed cardiopneumatic pathology (Brunshidle *et al.*, 2003). *Because of the tiny size of the UFP, these can penetrate the lung epithelium and enter the bloodstream. From there, particles can be transferred to liver, bone marrow, brain and heart, leading to a systematic infection.* Studies in dogs have confirmed this evidence. Studies in rats have shown a significant transfer of inhaled UFP to the liver (Brunshidle *et al.*, 2003).

The particles *deposit in the lung* with one of the 4 following ways (CCOHS, 1999); *Interception:* A particle deposits by interception when it moves so close to the airway surface that the edge of the particle touches the surface. This deposition method is the main method for fibres such as asbestos. The length of the fibre determines the point where the particle will be intercepted and deposit. For example, fibres of 1μm diameter and 200μm length will be deposited in the bronchial tree; *Impaction:* When particles are suspended, they tend to travel alongside their original course. When a bend appears in the airways, for example, many particles do not spin, but rather crash or attach to a surface along their initial course. Impaction probability depends on air velocity and particle mass; *Sedimentation:* While particles travel with air, gravity forces and air resistance finally overcome their buoyancy (particle tendency to stay afloat). This results in particle deposition in a lung surface. This type of deposition is most common for bronchi and bronchioles. Sedimentation is not an important factor when the aerodynamic diameter of the particle is less than 0.5μm. This is primarily the deposition mode for particles larger than 0.5μm. The use of aerodynamic diameter allows the experts to compare particles of different size, shape and density with regards to how they will settle out of the air flow stream; *Diffusion:* The random movement of the particles is similar to gas molecules in the air when the particles are less than 0.5μm. When the particles move randomly, they deposit on lung walls mainly by chance. This transfer motion is also known as Brownian motion[2]. The smaller the particles, the more vigorous the transfer motion is. Diffusion is the primary deposition mode in the small airways and the alveoli.

Depending on their size, UFP could deposit in nasal, tracheobronchial and alveolar regions by diffusion. As we observe from Figure 1, 90% of inhaled UFP close to 0.001μm in size deposit in the nasopharyngeal cavity (Swift *et al.*, 1992; Cheng *et al.*, 1996). Only 10% of the same size UFP deposit in the tracheobronchial regions and 0% (none) in lung alveoli. In control, UFP of 0.005 to 0.010μm in size deposit in all three lung regions with about 20-30% efficiency in every one. As far as UFP sizes 0.020μm are concerned, 50% of them deposit in alveolar region and only 10% in the tracheobronchial region and 10% in the nasopharyngeal cavity (ICRP, 1994). Therefore, we conclude that every one of the 3 lung regions is targeted differentially from the different sizes UFP (Figure 2). Their fate following deposition in the respiratory system seems to differ from that of coarse particles, at least with regards to solid and poorly soluble UFP (Oberdorster *et al.*, 2003).

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[2] *Brownian Motion:* This movement is owed by the collision of molecules of the air to very small suspended particles. The final movement of particles is accidental and distressed.

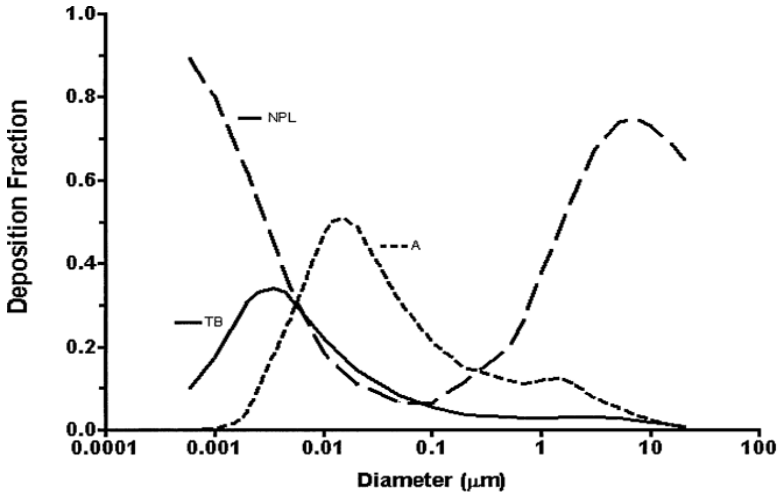

Figure 1. Model for fractional deposition of inhaled particles ranging from 0.006μm to 20μm in the nasopharyngeal region and the larynx (NPL0, in the tracheobronchial (TB) and alveolar (A) region of the human respiratory tree during nasal breathing. Please note that in the ultrafine size range (<0.1μm) there are significant differences among the 3 regions as far as particle deposition probabilities are concerned.
(Oberdorster *et al.*, 2003 taken from IRCP, 1994)

3. BIOLOGICAL MARKERS OF THE DISEASE

UFP inhalation is known to definitely affect two organ systems, the heart and the lungs. The lungs are affected by inhalation of carbonaceous[3] UFP, which penetrate deep in the lung and deposit in the alveoli. Particles also deposit in the lung epithelium and can translocate to the intercellular space. Then, particles induce an inflammatory reaction. This inflammatory reaction can be measured by the number of polynucleated lymphocytes during pulmonary lavage, as shown in study with rats (Brunshidle *et al.*, 2003). The extent of the reaction can be verified not by the amount of material retention in the lungs but by the occupied surface (Oberdorster, 1996). This inflammatory reaction appears as a series of events having health adverse effects, as found in another rat study. According to the Orberdorster model (Oberdorster, 1996), exposure to particulate matter leads to alveolar macrophage activation leading to acute inflammation and decreased removal. This results in acceleration of particle accumulation leading to chronic inflammation. This can cause lung fibrosis as well as mutations followed by epithelial cell hyperplasia. This, in turn, can induce metaplasia and tumour formation. In rats, the final stage could be carcinogenesis.

4. RESEARCH

4.1 Epidemiological Studies

In general, epidemiological studies attempt to correlate exposure to particulate matter (PM) with health effects, by examining (Morawska *et al.*, 2004); particulate matter characteristics (e.g. size, concentration, composition) that could be responsible for the mortality and morbidity effects; social and medical factors that could aggravate the health risks when particle pollution increases; and possible pathophysiological mechanisms that could lead to death when humans are exposed to air particulate pollution.
A summary of the key epidemiological studies associating health effects with ultrafine particles is presented in Table 1. The great majority of these studies were conducted within the framework of European *ULTRA* program by a group of researchers from Finland, Germany and the Netherlands.

[3] *Carbonaceous*: Organic and inorganic carbon compounds.

Table 1. Summary of epidemiological studies on health effects from ultrafine particulate matter (UFP) exposure

REFERENCES (LOCATION OF STUDY)	PARTICLE TYPES	EXPERIMENTAL GROUPS	EFFECTS EXAMINED	FINDINGS AND CONCLUSIONS
Osunsanya *et al*., 2001 (UK)	• PM_{10} • UFP	44 adults (>50 years old) with chronic pulmonary disease	Respiratory symptoms	No association was found between UFP, respiratory symptoms and peak expiratory flow (PEF). A correlation was found between PM_{10} and respiratory symptoms.
Pekkanen *et al*., 2002 (Finland)	*Size* • FP • UFP *Mass* • PM_1 • $PM_{2.5}$ • M_{10}	45 adults with coronary disease	Cardiovascular symptoms	Independent correlations were observed between FP and UFP, at a ST segment depression risk during repeated trials. No correlation was found for the coarse particles. The correlations tended to be stronger between people that did not use β-blockers. *Conclusions:* The results showed that the effect of atmospheric particle pollution on cardiovasuclar symptoms is at least indirect by increasing the sensitivity to myocardiac ischaemia.
Penttinen, 2001 (Finland)	*Size* • FP • UFP *Mass* • PM_1 • $PM_{2.5}$ • PM_{10}	54 asthmatic adults, non-smokers	Respiratory symptoms	The daily average arithmetic particle concentration, but not their mass, was negatively connected with daily divergences PEF. The largest effects were seen with UFP. However, the UFP effects could not be clearly isolated from other traffic pollutants, such as nitric oxide, nitrogen dioxide and carbon monoxide. No correlation was found for respiratory symptoms or medicine use. Particle mass measurements could be strongly affected by mechanically or soil produced particles that cannot be correlated with health adverse effects. Therefore, monitoring air quality should include particle number concentration, which primarily reflects the UFP.
Wichmann *et al.*, 2000 (Germany)	*Size* • FP • UFP *Mass*[4] • $PM_{2.5}$ • PM_{10}	General population	Cardiovascular & Respiratory mortality	It was established that FP and UFP are associated with increased mortality. However, the PF had more direct effects compared to the UFP, which showed a four-day delay in the concentration-mortality relationship. Furthermore, the direct results were more evident in respiratory cases, while the delayed effects were more evident in cardiovascular cases. *Conclusions:* FP could be used as an index for UFP. Moreover, UFP concentration seems to continually increase from 1991/92 while FP appears to decrease.

4.2. Clinical Studies

The controlled exposure studies referred in this chapter fall in two categories. The first category is related with dosimetry. The dosimetry studies are shown in Table 2. These studies have assessed different dosimetric aspects of ultrafine particle inhalation including the possibility of crossing the air-blood lung barrier and the resulting pathological consequences. The second category of the studies belongs to the *Frampton*-proposed type. These examine

[4] Measured from particle number.

whether and up to which point the inhaled ultrafine particle can cause acute lung damage or/and inflammation as well as other non-respiratory health adverse effects. These studies are shown in Table 3.

Table 2. Dosimetry

REFERENCES	RESEARCH OBJECTIVE	EXPERIMENTAL GROUPS	EXPOSURE DETAILS	RESULTS
Brown *et al.*, 2002	To characterize the deposition and removal of UF particles (technetium-99m) in COPD patients and healthy volunteers.	*COPD* 6 ♀ 4 ♂ 45-70 years old Divided in bronchitis and emphysema subgroups *Healthy* 6 ♀ 3 ♂ 40-67 years old	Inhalation through a mouthpiece Technetium particles-99 m CMD= 0.033±2μm Inhalation continued until 25mCi were deposited in the lung	*Scintigram* • No hepatic accumulation • Removal was not significantly different between healthy and COPD groups • The C/P_0 index increased in the bronchitis subgroup of the COPD group compared to the healthy group *Deposition* • Significantly greater in bronchitis subgroup compared to the healthy and emphysema subgroups.
Kim and Jaques, 2000	To find data for human lung region –dose relationship	11 ♀ 11 ♂ 20-40 years old Non-smokers or non-smokers the last 5 years	Inhalation through a mouthpiece. Bolus dose of oil particles condensed in metallic nuclei Particle size of 0.04, 0.06, 0.08 and 0.1 μm Respirable volume 500ml and flow rate 250 ml s^{-1}	Regional deposition varies greatly along the depth of the lung independent of molecule size.

4.3. Toxicological Studies

In-vivo animal studies conducted in live animals demonstrate that there is a greater tendency for generation of inflammation following ultrafine particle (UFP) exposure. This result, as seen with the aforementioned studies, correlates with increased particle surface area. These studies are shown in Table 4.

In-vitro animal studies (Table 5) have examined several different cell types from animals as well as humans. In all cases inflammation was the end-point assessed. In studies where DEP were included, the results seem to primarily associate with the absorbed compounds. These studies also showed that particles persist in tissues as relatively large groups of single particles. The smaller the particles the easier for them to penetrate the epithelium. The particles are also capable of increasing inflammatory cytokine production. Agents such as interleukin – 8 and interleukin – 10 are produced. However, *in-vitro* studies do not allow the assessment of the complex interactions of these cytokines since they are conducted on simple cell types and do not assess the intracellular mechanisms that determine the operations of these agents in the whole organism. As with other studies, the determining factor for the effects of ultrafine particles is the particle surface area and not their weight.

Table 3. Controlled exposure studies to ultrafine particles (UFP)

REFERENCES	RESEARCH OBJECTIVE	EXPERIMENTAL GROUPS	EXPOSURE DETAILS	RESULTS
Frampton *et al.,* 1992	To determine whether exposure to H_2SO_4 particles induces alveolar reaction	2 ♀ 10 ♂ Healthy, non-smokers 20-39 years old	• Gas chamber exposure • H_2SO_4 particles with average diameter 0.9 μm • Exposure during exercise • Double-blind study	*Symptoms* • Four detected an odor • Three had cough and four felt discomfort in the neck during exposure *Plethysmography* • No change in FVC and FEV_1 immediately or 18 hours following exposure *Bronchoalveolar lavage* • No significant difference in various cell counts *Alveolar macrophage function* • No statistical difference was found in macrophage function
Holgate *et al.,* 2002	To assess the effect of short-term exposure to diesel exhausts on induction of airway inflammation. The objective of the study was to assess whether the observed increased sensitivity to atmospheric pollutants in asthmatics could be explained by neutrophil-mediated inflammation or/and enhanced effect of airway inflammation, due to diesel exhaust exposure	*Asthmatic group* 5 ♀ 10 ♂ 23-52 years old Mild non-local asthma Sensitivity to at least one suspended allergen Non-smokers *Control group* 9 ♀ 16 ♂ 19-42 years old Normal lung function No allergen sensitivity	• Gas chamber exposure • Diesel exhaust exposure • Double-blind study	*Lung function* • A mild but statistically significant increase in airway resistance at the end of exposure in the asthmatic group • A mild but statistically significant increase in airway resistance at the end of and one hour after exposure in the control group • No significant change in FVC or FEV_1 *Peripheral blood:* • No significant change Cleared blood before and after exposure *Bronchoalveolar lavage:* • Significantly more neutrophils in the control but not the asthmatic group • Significantly higher IL-6 and IL-8 levels in the control but not the asthmatic group • Significantly higher leukocyte counts in the control group • Significantly lower macrophage counts in the control group
Salvi *et al.,* 1999	To test the hypothesis that diesel exhaust exposure can induce inflammatory reactions in airways and peripheral blood	4 ♀ 11 ♂ 21-28 years old Healthy non-smokers	• Gas chamber exposure • DEP and PM_{10} particles and clean air (control) • Blind study	*Spirometry:* • No statistical difference in the parameters *Peripheral blood:* • In the DEP exposed group, the neutrophils and platelets were increased • In the DEP-exposed group the cellular HLA-DR^+ was found less *Bronchoalveolar lavage:* • In the DEP exposed group there was a significantly greater neutrophil number

Table 4. Summary of in-vivo animal studies

REFERENCES	EXPERIMENTAL GROUPS	EFFECT	RESEARCH STUDY DESCRIPTION	FINDINGS - CONCLUSIONS
Baggs *et al.,* 1997	Rats	Inflammation (Lungs)	344 rats were exposed for six hours daily, 5 days a week, for 3 months to 1) filtered air (control) 2) TiO_2-D, particle size 0.02μm 3) TiO_2-F, 0.25μm 4) Crystal SiO_2, 0.8μm	Within 6 months following exposure: • In SiO_2, there was mild focal interstitial fibrosis and serious focal alveolitis • In TiO_2-D and TiO_2-F, there was slightly less fibrosis. Within 1 year following exposure: • the fibrosis was still present but decreased in the SiO_2 group • the percentage of interstitial fibrosis, due to treatment with TiO_2-D and TiO_2-F, returned to pre-treatment levels *Conclusions:* Inhaled UFP TiO_2-D lead to greater lung inflammatory response compared to larger particles.
Brown *et al.,* 2001	Rats	Respiratory	Examined pre-inflammatory reactions to different polystyrene particle size	There was significantly greater neutrophil inflow to the lung following instillation of polystyrene particles 0.064μm compared to 0.202 and 0.535μm particles. *Conclusions:* The results suggest that UFP composed of low-toxicity material such as polystyrene induce pre-inflammatory activity due to their large surface area.
Osier & Oberdorster, 1997	Rats	Inflammation	Rat reaction to inhalation exposure (endotracheal) of FP (0.25μm) and UFP (0.021μm) titanium dioxide was compared to rats exposed to similar doses of endotracheal instillations.	The animals exposed to particles through inhalation showed decreased respiratory reaction (measured from bronchoalveolar lavage), both in the seriousness and persistence, compared to rats exposed to instilled particles. These differences could be accounted by variations in dose, particle distribution or differential removal between the two routes of administration.
Takenaka *et al.,* 2000	Rats & *in-vitro* (macrophage cells)	Inflammation	The fate of UFP aggregates (Ag) was examined in macrophages, in the dish and in the live organism.	Both in the dish and the live organism, the studies showed that Ag particle aggregates remained in their targets for a period at least 7 days.

5. UFP IN BRAIN AND CENTRAL NERVOUS SYSTEM

In 2002, Oberdorster et al, presented the hypothesis that UFP could enter the brain and central nervous system (CNS). This could occur through some type of nerve (e.g. olfactory) or through the blood-brain barrier or through some other way (Oberdorster and Utell, 2002). Depending on their size, UFP could deposit in nasal, tracheobronchial and alveolar regions by diffusion. Previous studies in rats and mice have showed that UFP could transfer to interstitial space in the pulmonary system as well as in extra-pulmonary systems, such as the liver, 4 to 24 hours following exposure. There are also indications that the olfactory bulb in the brain is a target. It was found in a pilot study with inhaled ^{13}C UFP that there is a significant increase of ^{13}C in the rat olfactory bulb, which led to the hypothesis that there are other translocation

routes of solid UFP besides the blood stream. These could be neural pathways from nasal olfactory mucosa deposition via the olfactory nerve (Oberdorster *et al.*, 2003).

In the following Table 6 we see a summary of studies concerning the possible transfer of ultrafine particles to the brain and central nervous system.

Table 5. Summary of in-vitro animal studies

REFERENCES	EXPERIMENTAL GROUPS	EFFECT	RESEARCH STUDY DESCRIPTION	FINDINGS AND CONCLUSIONS
Beck-Speier *et al.,* 2001	*In-vitro* (immunized cells)	Non-immune cellular reactions	The response of non-immune cells to exposure to 0.077μm elemental carbon aggregates and titanium dioxide particles 0.021μm was assessed, by the release of lipid mediators from alveolar macrophages.	The results show that the surface area rather than mass concentration determines the effects of UFP
Boland *et al.,* 2000	*In-vitro* (human bronchial epithelial cells)	Inflammation (Lungs)	The mechanisms behind the increase and release of GM-F, detached from DEPs, were studied	The increase in GM-F release came primarily from available organic compounds and the effect of intrinsic DEP requires particle endocytosis
Kawasaki *et al.,* 2001	*In-vitro* (human cells)	Inflammation (Lungs)	The pre-inflammatory effects of DEP on the respiratory track were studied.	It was established that DEP increased cytokine (inflammatory mediators) production from human epithelial cells of airways
Kim *et al.,* 2003	*In-vitro* (collagen gel)	Inflammation	The three-dimensional collagen gel contraction template was used to assess whether carbonated UFP could affect tissue repair	The results show the ability of UFP to alter the tissue repair process
Stone *et al.,* 2000	Rats	Inflammation	It was examined whether UFP could induce alterations in calcium flow in macrophages	BC UF particles are likely to activate calcium flow, partially through oxidative pressure.
Timblin *et al.,* 2002	*In-vitro* (alveolar epithelial cells)	Inflammation	The dose-dependent proliferation and apoptosis after exposure of alveolar epithelium to PM or UFCB or to a PM component was illustrated.	It was established that the ultrafine size of particulate matter is very important for its bio-activity.
Wilson *et al.,* 2002	*In vitro*	Inflammation	The interactions between transition salts and UFCB were measured	In all experimental systems used, the ultrafine carbon black was found to be more active than the respective fine.

Table 6. Studies related to UFP translocation to the Brain and CNS

REFERENCES	EXPERIMENTAL GROUPS	RESEARCH EVIDENCE	FINDINGS AND CONCLUSIONS
Dorman *et al.*, 2004	Rats	*Particles:* Mn sulfate Mn phosphate	• No indication of alteration in brain GFAP levels following exposure. • Mn transfer to the olfactory bulb, cerebellum and striatum was measured. A small increase in Mn content was found only in the olfactory bulb.
Henriksson and Tjalve, 2000	Rats	*Particles:* Mn chloride Nasal instillation	Changes in Glial Fibrilliary Acidic Protein (GFAP) and S-100b were reported, markers of astrocyte activation in different brain regions.
Oberdorster *et al.*, 2004	Rats	*Particles:* ^{13}C, 0.035μm Inhalation and full body exposure	Particle accumulation in the olfactory bulb was observed.
Tjalve *et al.*, 1995	*Esox Lucius*	*Particles:* Non – ionic Nasal instillation	Ionic Mn was shown to have the ability to pass through synaptic junctions and migrate from the olfactory region to more distant regions, including the hypothalamus.
Tjalve *et al.*, 1996 Henriksson and Tjalve, 1999	Rats	*Particles:* Mn compounds Inhalation or/and full body exposure	Mn compound transfer was observed from the nose through the olfactory nerve axons to the olfactory bulb.
Bodian and Howe 1941a; 1941b DeLorenzo 1970	Non-human mammals	*Particles:* Polio virus, 0.030μm & Collagen-like 0.050μm	Transfer ability of solid ultrafine particles was shown alongside axons of olfactory nerves to the olfactory bulb.

6.FINDINGS AND CONCLUSIONS

The epidemiological studies have provided evidence that there is serious health hazards associated with the human exposure to environmental levels of particulate matter found in the urban centres at concentrations below the acceptable particulate matter levels (US EPA, 1996). Even though various reactions to components of environmental particulate matter have been hypothesized to contribute to the reported health hazards, the related published toxicology and controlled human clinical studies have not pinpointed an acceptable mechanism that could explain how such low levels of particulate matter concentration could cause the health hazards reported in the epidemiological studies. However, the toxicology studies tend to show that particles become more toxic per mass unit with decreasing size. This makes UFP a primary target for further research. Consequently, our attention turns to the surface area or the particle number, rather than mass concentration.

The studies on particle mass concentration (PM_{10} and $PM_{2.5}$) show that there is no lower limit for particle mass below which there is no health danger. This is presented in the guidelines of the World Health Organization for air quality (WHO 1999b), which has a linear relationship between PM_{10} and $PM_{2.5}$ with various health indicators (including mortality, hospital admissions, bronchodilators use, symptom aggravation, cough and peak expiratory flow) for concentration levels from 0 to 200 μg m^{-3}.

To summarize part of the aforementioned knowledge, the following Table 7 includes the systems in which the particles could be accumulated, most of the known signs, symptoms and diseases that born or altered by human exposure to suspended particulate matter, and especially, ultrafine particles.

Table 7. Possible effects of PM in human systems

System	Possible Effects
Respiratory System	• Some epidemiological studies showed adverse effects only in compromised people. • Changes in lung function and increase in respiratory pathologic symptoms. • Changes in lung histology and structure • Changes in respiratory immune mechanisms • Asthma exacerbation • Chronic bronchitis • Pulmonary system infection • Macrophage, neutrophil and monocyte concentrations were significantly greater in the bronchoalveolar lavage of exposed people • Significantly higher IL-6 and IL-8 levels in the bronchoalveolar lavage of exposed people • Significantly higher leukocyte counts in the control group in the bronchoalveolar lavage of exposed people • Mild focal interstitial fibrosis • Inflammatory reaction in the lung • Lung disease exacerbation (as corroborated by increased numbers of hospital admissions, visit to emergency room, school absences, missed work-hours, days of reduced activity due to health problems) • Maybe alterations in FEV_1, FVC and PEF and spirometry • Increased respiratory morbidity and mortality in sensitive populations
Cardiovascular System	• The whole process predisposes the person to cardiovascular damage: 1. Damage in epithelial cells from reactive oxygen species and activation of regulation factors. 2. Activation of vascular endothelium and circulatory polymorphonuclear leukocytes. 3. Inflammatory cell migration from the blood to tissues. 4. Up-regulation of adhesive molecules in vascular endothelium. 5. Increased secretion of interleukin – 6 (IL-6) and tissue factors through activation of blood factors. 6. Mononucleated cells activate C-reactive protein (CRP), amyloid A and fibrinogen. • Cardiac ischemic disease • Heart attack • ST segment depression risk • Increasing the sensitivity to myocardial ischemia. • Heart disease exacerbation (as corroborated by increased numbers of hospital admissions, visit to emergency room, school absences, missed work-hours, days of reduced activity due to health problems) • Increased cardiovascular morbidity and mortality in sensitive populations
Gastrointestinal System	• UFP are related to Crohn's disease (chronic recurrent inflammatory intestinal disease). • UFP, deposited and accumulated in the Liver • UFP, deposited and accumulated in the bladder
Circulatory System	• Changes in blood indicators • UPF penetrate very deep and fast in the interstitial space and could enter blood circulation
Nervous System	*CNS* • Mn ultrafine particles translocated to the olfactory bulb, cerebellum and striatum • Particle accumulation in the olfactory bulb was observed • Ionic Mn was shown to have the ability to pass through synaptic junctions and migrate from the olfactory region to more distant regions, including the hypothalamus • Transfer ability of solid ultrafine particles was shown alongside axons of olfactory nerves to the olfactory bulb *ANS* • Alterations in Autonomic Nervous System (ANS) function, and changes in cardiovascular risk factors such as arterial blood pressure, C-reactive protein and endothelial dysfunction
Urine	Thin layer chromatography (TLC) showed the presence of a soluble ^{99m}Tc type and the absence of any ^{99m}Tc type bound to carbon particles
General Symptoms	• Cough • Fatigue • Muscle aches • Discomfort in the neck • Premature mortality

From the above comprehensive literature review, we conclude that there is a correlation between UFP and alterations in morbidity and mortality indices because of respiratory and cardiac effects in the elderly and susceptible groups. There is also a correlation with increased proportion of asthma episodes and hospital admissions. Ultrafine particle (UFP) exposure could be responsible for increased medicine use, missed work-hours and school absences.

Of course, it is not only the respiratory and cardiovascular system that have been hypothesized and studied as target systems of ultrafine particles (UFP). The past few years, researchers throughout the world generate more and more data suggesting that the exposure of the human body to UFP effects could be widespread. The size of the specific particulate matter allows its penetration to system blood stream. Organs, such as the liver, could also be considered as organ-targets according to recent studies. What is most impressive and scientifically challenging is the latest evidence suggesting possible penetration of particles of this size (UFP, <0.1μm) to the brain and central nervous system.

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