*Task force report*

# A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): Why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects

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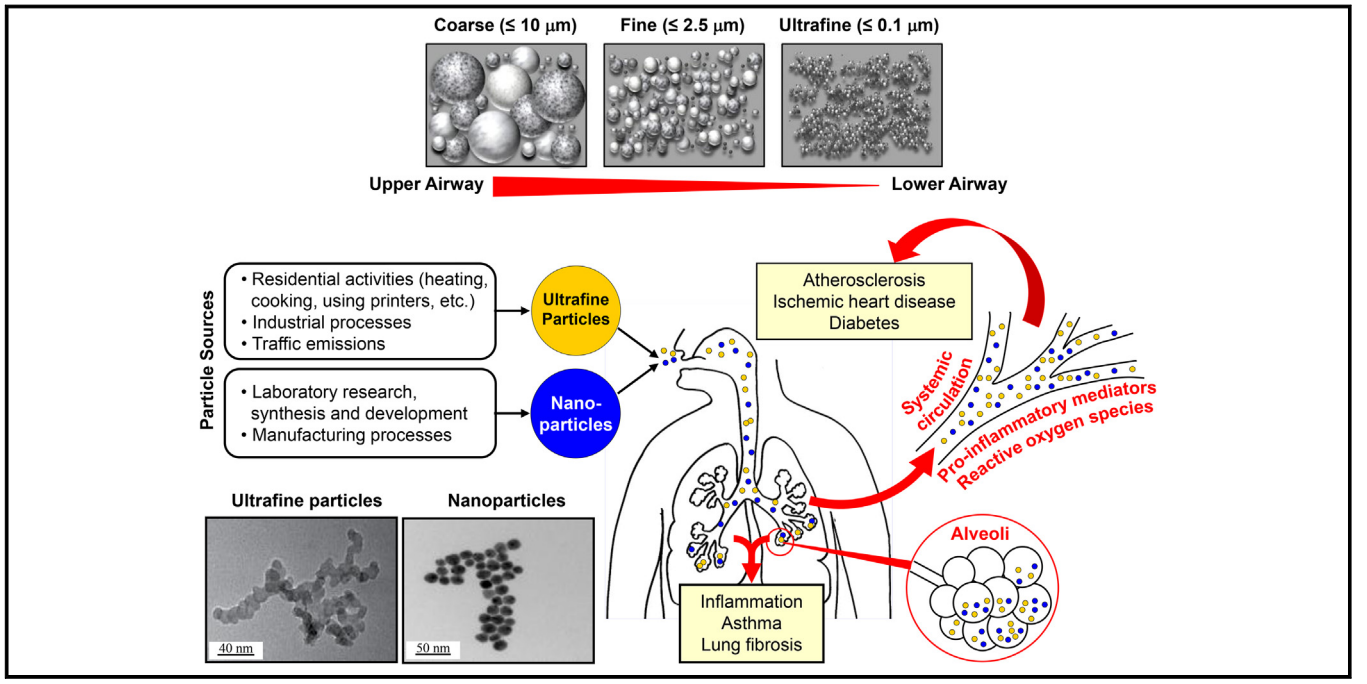
## GRAPHICAL ABSTRACT

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The electron micrograph of ultrafine particles in the graphical abstract is reprinted with permission from *Science* (Reference 2 in the article).

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**Ultrafine particles (UFPs) are airborne particulates of less than 100 nm in aerodynamic diameter. Examples of UFPs are diesel exhaust particles, products of cooking, heating, and wood burning in indoor environments, and, more recently, products generated through the use of nanotechnology. Studies have shown that ambient UFPs have detrimental effects on both the cardiovascular and respiratory systems, including a higher incidence of atherosclerosis and exacerbation rate of asthma. UFPs have been found to alter *in vitro* and *in vivo* responses of the immune system to allergens and can also play a role in allergen sensitization. The inflammatory properties of UFPs can be mediated by a number of different mechanisms, including the ability to produce reactive oxygen species, leading to the generation of proinflammatory cytokines and airway inflammation. In addition, because of their small size, UFPs also have unique distribution characteristics in the respiratory tree and circulation and might be able to alter cellular function in ways that circumvent normal signaling pathways. Additionally, UFPs can penetrate intracellularly and potentially cause DNA damage. The recent advances in nanotechnology, although opening up new opportunities for the advancement of technology and medicine, could also lead to unforeseen adverse health effects in exposed human subjects. Further research is needed to clarify the safety of nanoscale particles, as well as the elucidation of the possible beneficial use of these particulates to treat disease. (J Allergy Clin Immunol 2016;138:386-96.)**

***Key words:*** *Ambient ultrafine particles, engineered nanoparticles, particle deposition and distribution, allergic inflammation, asthma, lung inflammation, oxidative stress, effect on human health*

*Abbreviations used*

AgNP: Silver nanoparticle
CNT: Carbon nanotube
DC: Dendritic cell
EC: Elemental carbon
ENM: Engineered nanomaterial
MWCNT: Multiwall carbon nanotube
OC: Organic carbon
OVA: Ovalbumin
PAH: Polycyclic aromatic hydrocarbon
$PM_{2.5}$: Particulate matter with an aerodynamic diameter of less than 2.5 μm
$PM_{10}$: Particulate matter with an aerodynamic diameter of less than 10 μm
ROS: Reactive oxygen species
$TiO_2$: Titanium dioxide
UFP: Ultrafine particle
ZnO: Zinc oxide

Compared with our understanding of the health effects of particulate matter with an aerodynamic diameter of less than 10 μm ($PM_{10}$, coarse PM) and less than 2.5 μm ($PM_{2.5}$, fine PM), there is a considerable knowledge gap about the effect of particles of less than 100 nm on human health. Increasing evidence from air pollution and nanosafety research suggests these submicron-scale particles have physicochemical properties significantly different from those of larger PM and therefore might exert adverse health effects, including promoting asthma exacerbation and allergic sensitization to common allergens, through different mechanisms (Table I).[1,2] Currently, these particles are classified into 2 major categories based on their sources. Ultrafine particles (UFPs) refer to the particles that are incidentally generated in the environment, often as byproducts of fossil fuel combustion, condensation of semivolatile substances, or industrial emissions, whereas nanoparticles are manufactured through controlled engineering processes.[1] Although there are many differences in the physicochemical composition of UFPs and nanoparticles, one common feature is their extremely small size; this allows these particles to have unique characteristics that can cause harmful health effects to human subjects (Box 1 and Table II).[1]

In 2013, the Health Effects Institute Review Panel concluded, based on the database available at that time, that there was no evidence that the adverse health effects of UFPs were dramatically different from those of $PM_{2.5}$. However, epidemiologic and clinical trial studies published in 2014 and 2015 question this conclusion (see below for further discussion).[3-9] Moreover, experimental evidence suggests that UFPs might be more dangerous than $PM_{10}$ and $PM_{2.5}$ because of their chemical composition, small size, large surface area/mass ratio, capability of generating reactive oxygen species (ROS), high retention rate, and deep penetration in the respiratory system.[10,11]

Several key facts indicate a critical need to address the adverse health effects of ambient UFPs. First, although $PM_{10}$ and $PM_{2.5}$ can be removed easily through phagocytosis, the extremely small size of UFPs enables them to evade such host defense and deposit in the lung with a high rate of retention. Thus, for the same volume of air inhaled, the actual dose and regional effects of UFPs in the lung might be significantly greater than that of $PM_{2.5}$. Moreover, the size of UFPs allows them to translocate to other organs through the systemic circulation, leading to toxicological mechanisms that are very different from those of $PM_{2.5}$.

Second, the large surface area enables UFPs to carry large quantities of adsorbed hazardous materials on a per-mass basis, including organic chemicals and metals that can generate ROS and oxidative stress. Oxidant injury plays an important role in UFP-induced adverse health effects, including exacerbation and promotion of asthma, chronic obstructive pulmonary disease, and atherosclerosis.[11-14]

Third, unlike $PM_{2.5}$, UFPs are not homogeneously distributed in the atmosphere but rather localized in hot spots of exposure (eg, near roads with busy traffic). This has resulted in a lack of extensive UFP monitoring networks and limited epidemiologic studies, a situation that is unlikely to change until regulatory agencies decide to track these particles as criteria pollutants.

Fourth, the composition of semivolatile organic compounds on the UFP surface can vary dynamically depending on the source and molecular size, challenging efforts to draw simple conclusions about their health effects.

Fifth, although the health effects of $PM_{10}$ and $PM_{2.5}$ are determined based on PM mass, the "weightless" nature of UFPs requires other exposure metrics (ie, particle number and surface area). Unfortunately, epidemiologic studies using these metrics are currently limited.

Finally, although improved engine and fuel technologies have significantly reduced the emission of particulate soot, UFPs can still be formed from vapor condensation and they can be even