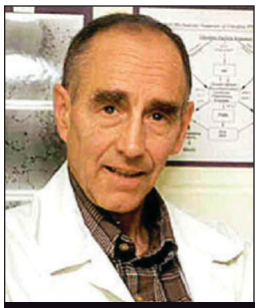
Is the central nervous system yet another target organ for ultrafine particles?

Ultrafine Particles in the Urban Air: To the Respiratory Tract—And Beyond?



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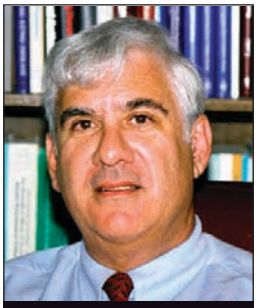

Mark J. Utell

In 1994, when we introduced the ultrafine particle hypothesis stating that ambient ultrafine particles (UFP; < 0.1 μm in aerodynamic diameter) may cause adverse health effects at the first Colloquium for Particulate Air Pollution and Human Mortality and Morbidity in Irvine, California, it was met with friendly skepticism as well as out-right dismissal. Arguments were that UFP are very short-lived and disappear through heterogeneous and homogeneous aggregation within seconds or minutes and therefore are toxicologically irrelevant. These arguments did not recognize that UFP are continuously generated or that ambient UFP contribute very little, if any, mass to ambient PM_{10} (particles < 10 μm in aerodynamic diameter) or $PM_{2.5}$ (particles < 2.5 μm in aerodynamic diameter). Indeed, the mass distribution of a typical urban aerosol among the different particle sizes may support this point (Figure 1). This attitude of skepticism has changed considerably. Research teams across the world are working now on UFP, forming multidisciplinary alliances between atmospheric scientists, engineers, epidemiologists, clinicians, and toxicologists. They investigate UFP sources, generation, physicochemical characteristics, behavior in ambient air, and potential effects and underlying mechanisms following their inhalation. Still, sound skepticism lingers, as demonstrated by the title of a presentation at the 2002 meeting of the Health Effects Institute: "Nanoparticles: Are They Real?"

Obviously, there is no question that UFP are real, but it is also clear that we still do not know enough about them, despite significant progress in our understanding since 1994. Atmospheric UFP derived from gas-to-particle conversions have many sources, natural and anthropogenic, the latter being mostly derived from internal combustion processes. Diesel fuel, gasoline, and even compressed natural gas—considered to be "clean"—powered engines all emit high numbers of UFP. If these anthropogenic UFP cause significant health effects, is the conversion of diesel-powered buses to compressed natural gas—as practiced now in several cities—really a good idea? We should be more cautious about introducing technologies based on the assumption that they result in cleaner air with fewer and less toxic contaminants. The experience with methyl *tert*-butyl ether as a fuel additive should serve as a reminder of the potential unintended health and environmental consequences of altering fuels and resulting emissions on a large scale without an adequate understanding of toxicity.

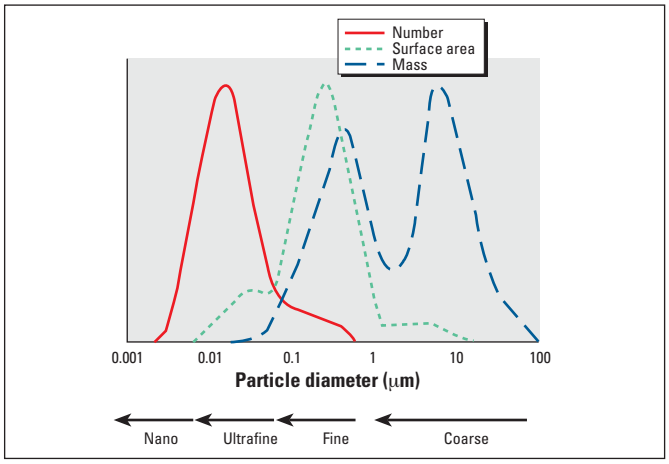

Figure 1. Typical urban particle size distribution based on the work of Finlayson-Pitts and Pitts (2000). In this editorial, ultrafine particles are considered to be those < 0.1 μm, but there is no general consensus about this definition; the term "nanoparticles" has also been used for particles < 0.01 μm, as shown.

Since vehicular emissions are regulated by mass output, modern technologies for internal combustion engines favor the generation and formation of UFP because they contribute minimally to the mass output of fine particles (Figure 1). It should come as no surprise that "clean" engines are built to conform to present standards of mass output, despite emitting high numbers of UFP. A standard based on particle number would be more appropriate to reduce UFP emissions. A standard based on particle surface area—as is also proposed—may not be helpful to control UFP because fine particles comprise most of the total particle surface area (Figure 1). In recent measurements made during road-chase studies in Minnesota, UFP concentrations were as high as 1×10^7 particles/cm^3 (Kittelson et al. 2001). A short distance from the highways, these high UFP concentrations are lower, but individuals in automobiles on the highways are directly exposed to the high concentrations. Moreover, these UFP are freshly generated, and if results of earlier toxicologic studies with UFP generated from thermodegradation products of polymers are an indication of a general principle of UFP toxicity, freshness and proximity to the source are key requirements for inducing acute adverse effects of UFP.

Do UFP emitted from internal combustion engines cause adverse health effects? We still need to know more, but results from our controlled clinical and animal studies using ultrafine elemental carbon particles permit some preliminary conclusions: The high deposition of inhaled UFP (0.007–0.1 μm) in the human respiratory tract as predicted by ICRP (1994) could be confirmed; moreover, deposition was even higher during exercise and in asthmatics. Unlike larger fine particles, UFP seem to escape phagocytosis by alveolar macrophages and are translocated to extrapulmonary organs, as was determined in rodents using ultrafine ^{13}C particles, although such translocation was only minimal with ultrafine iridium particles. Cardiovascular effects in humans and animals and mild pulmonary inflammation in animals were also found following ultrafine carbon particle exposures.

Although health effects data and understanding of mechanisms are still limited, there are intriguing data from other disciplines, in particular the field of drug delivery: Intravenously administered UFP were found to cross the blood–brain barrier (Kreuter, 2001), and a transport function of caveolae for macromolecules with molecular radii of several

nanometers across the alveolar–capillary barrier as a pathway for protein delivery from lung to blood seems to exist (Gumbleton, 2001); could this be a mechanism for solid UFP transport as well, given that the openings of the caveolae range between 0.04 and 0.1 µm? Intriguing as well is the apparent existence of still another, more direct, pathway of UFP deposited in the respiratory tract to extrapulmonary organs via neurons, including transsynaptic transport. This was first reported by Howe and Bodian (1940) for 0.03-µm polio virus in monkeys and was later described for nasally deposited colloidal 0.05-µm gold particles moving into the olfactory bulb of squirrel monkeys (de Lorenzo 1970). Ultrafine carbon particles may translocate along the same pathway to the central nervous system (CNS), based on our recent finding of these particles in the olfactory bulb of rats after their inhalation.

A fascinating question is whether the CNS is another target organ for inhaled UFP. If so, could this mean that some effects of UFP on cardiovascular function are mediated via the autonomic nervous system? In this context, Calderon-Garciduenas et al. (2002) reported significant histologic lesions in olfactory bulb and other brain regions and olfactory mucosa of dogs in Mexico City—with high air pollution—compared to dogs from a clean rural area. Their study did not establish a causal association between PM, or specifically UFP, and CNS effects, but it appears that the evidence is accumulating and becoming stronger that urban UFP are more than a nuisance.

The advances in our understanding of UFP kinetics and effects open many more questions, including evaluation of the importance of organic versus elemental ultrafine carbon particles; metal constituents of these particles with respect to their existence on the same or on different UFP; biologic/toxicologic activity of freshly generated versus aged ambient UFP; mechanisms of extrapulmonary transport; and direct versus indirect effects of UFP on extrapulmonary organs, including the CNS. With the emergence of so many unanswered questions, the health consequences of inhalation of UFP remain an important area of investigation.

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References and Notes

Calderon-Garciduenas L, Azzarelli B, Acune H, Garcia R., Gambling TM, Osnaya N, et al. 2002. Air pollution and brain damage. Toxicol Pathol 30(3):373–389.

De Lorenzo A, Darin J. 1970. The olfactory neuron and the blood-brain barrier. In: Taste and Smell in Vertebrates (Wolstenholme GEW, Knight J, eds). London:Churchill;151–176.

Finlayson-Pitts BJ, Pitts JN. 2000. Chemistry of the Upper and Lower Atmosphere: Theory, Experiments, and Applications. San Diego, CA:Academic Press.

Gumbleton M. 2001. Caveolae as potential macromolecule trafficking compartments within alveolar epithelium. Adv Drug Delivery Rev 49:281–300.

Howe HA, Bodian D. 1940. Portals of entry of poliomyelitis virus in the chimpanzee. Proc Soc Exp Biol Med 43:718–721.

ICRP. 1994. Human Respiratory Tract Model for Radiological Protection. A Report of a Task Group of the International Commission on Radiological Protection. ICRP Publication 66 (Smith H, ed). Ann ICRP 24(1-3).

Kittelson DB, Watts WF Jr, Johnson JP. 2001. Fine Particle (Nanoparticle) Emissions on Minnesota Highways. MN-RC-2001-12. St. Paul, MN:Minnesota Department of Transportation, Office of Research & Strategic Services.

Kreuter J. 2001. Nanoparticulate systems for brain delivery of drugs. Adv Drug Delivery Rev 47:65–81.