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SPECIAL FEATURE

Biological effects of fibrous and particulate substances and related areas

A current overview of health effect research on nanoparticles

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Abstract Nanotoxicology and nano-risk have been attracting increasing attention of toxicologists and regulatory scientists as the production of nanomaterials increases worldwide (Oberdorster et al. in Environ Health Perspect 113:823–839, 2005). In general, nanotoxicology is associated with manufactured nanomaterials. In atmospheric science and environmental health science, however, very small particles that exist transiently at high count concentrations near road intersections and roadsides are called environmental nanoparticles, and most of these have originated from automobiles. Accordingly there are two types of nanoparticle in toxicology and health science—environmental nanoparticles and manufactured or engineered nanoparticles. In this minireview I would like to address the following issues: (1) What is a nanoparticle? (2) Why is the nanoparticle currently a significant health issue? (3) How has "testing manufactured nanoparticles" been discussed worldwide? (4) What problems have scientists encountered in assessing the health hazard of nanoparticles? and (5) What research is required in the future in nanotoxicology?

Keywords Nanomaterial · Nanoparticle · Carbon nanotubes

What is a nanoparticle?

Manufactured nanoparticles are defined as particulate substances of nanoscale dimensions (usually <100 nm). In atmospheric science particles <100 nm have been called ultrafine particles and most atmospheric nanoparticles are usually <50 nm. It has been shown that the particle-count distribution peaks at 20–30 nm at roadsides with heavy traffic [2]. The differences between environmental and manufactured nanoparticles are summarized in Table 1. Environmental or atmospheric nanoparticles contain semi-volatile alkanes that originate from fuels and lubricants [3] whereas components of manufactured or engineered nanoparticles vary, depending on the type of product. It should be noted that nanoparticles are also used in drug-delivery systems (DDS), because nanoparticles can evade phagocytosis and efficiently reach the target points.

Why is the nanoparticle currently a significant health issue?

Diesel-exhaust particles (DEP) are usually black carbonaceous soots with particle dimensions 200–300 nm. They are major components of fine particles or PM2.5 (particulate substances less than 2.5 μm). Installing a diesel-particle filter (DPF) can reduce the number of larger particles in the exhaust. However, nanoparticles, which account for a much greater particle number concentration in the atmosphere than the larger particles, are produced during regeneration of the DPF. It has not been well investigated whether nanoparticles are responsible for pulmonary and extrapulmonary health effects of PM2.5, although the fine particles are reportedly associated with mortality from cardiovascular diseases [4]. Nanoparticles can permeate through tissue walls, translocate to other tissues from the deposition sites, and cause cardiovascular dysfunction. However, we do not have a clear answer as to whether nanoparticles have a distinctive toxicological aspect and are more toxic than larger particles.

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Table 1 Differences between environmental and manufactured nanoparticles

	Environmental nanoparticles	Manufactured nanoparticles
Size	≤50 nm (≤100 nm: ultrafine)	1–100 nm (biomedical nanoparticles can be larger than 100 nm)
Dimensions	Two or three dimensions are on the nanoscale	Three dimensions are on the nanoscale (nano-objects with one and two nanoscale dimensions are called nanoplates and nanofibers, respectively)
Names	Nanoparticles, fibrous nanoparticles	Nanoparticles, nanospheres, nanotubes, nanorods, nanofibers, nanowires, nanoropes, nanosheets, nanoeggs, nanoliposomes, dendrimers, etc.
Components	Carbon soot, hydrocarbons (alkanes), heavy metals, sulfur	Carbon (fullerene, nanotube), metal oxide (TiO_2, ZnO), CdSe, metalloids, transition metals, polymers
Sources	Automobile exhaust, friction, catalysts	Production of nanomaterials, cosmetics, friction

How has "testing manufactured nanoparticles" been discussed worldwide?

Two major international organizations have discussed guidelines for testing nanoparticles. The Organization for Economic Co-operation and Development (OECD) has published a series of guidelines for testing chemicals and those guidelines are generally accepted by many developed countries. The OECD has been struggling to decide whether current OECD test guidelines are applicable to human health and environmental aspects of nanoparticles or nanomaterials. The International Organization for Standardization (ISO) also has an Environment/Safety Working Group for nanomaterials. It may not be easy to apply current test methods to nanoparticles or nanomaterials, because most of these particles are insoluble and current guidelines are primarily designed for water-soluble substances or the water accommodated fraction (WAF) of poorly water-soluble substances.

What problems have scientists encountered in assessing the health hazard of nanoparticles?

There are many debates about the metric which best describes the toxicity of nanoparticles. The most commonly accepted dose metric is probably the surface area. Particle shape (e.g. fibrous or spherical), chemical composition, and the physico-chemistry of the particle surface, including the zeta-potential, are also important factors that determine the toxicity of nanoparticles. Also, impurities and the degree of agglomeration in the nanoparticle suspension in test media may affect the toxicity. An appropriate endotoxin-free medium should be chosen to prepare the suspension of nanoparticles [5]. In nature the nanoparticle has a large surface area which may function as adsorption or even catalytic sites and interfere in various bioassays.

What research is required in the future in nanotoxicology?

Exposure to nanomaterials should be assessed as soon as possible, because most nanomaterials are about to be produced on a large scale and some of these materials (e.g., nano-silver and nanosize titanium dioxide) are already present in commercial products. The environmental fate of nanoparticles should also be studied as a matter of urgency. Reference substances are required to evaluate the toxicity of nanoparticles and to prepare a proper test procedure. It has been reported that the carcinogenic potency and toxicity of asbestos [6, 7] and the toxicity of MWCNTs [8] largely depend on fiber length. Fibrous titanium dioxide particles have been shown to be much more cytotoxic than spherical nanosize titanium dioxide particles to alveolar macrophages [9]. Special attention should be paid to fibrous nanoparticles, because fiber length may be predominant metric determining the toxicity of biopersistent fibrous nanoparticles. An inhalation study, rather than intratracheal instillation, is needed to evaluate the toxicity of airborne nanoparticles, because nanoparticles agglomerate easily in suspension and toxicological outcomes from bolus injections of nanoparticles may differ significantly from those of dispersed nanoparticles.

The overall physico-chemical properties of nanoparticles/nanomaterials are important factors determining their toxicity. Nanotoxicology is a new research field and appropriate reference methods are required for assay of the toxicity of nanoparticles either in vitro or in vivo.

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