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Perspectives

Airborne nanostructured particles and occupational health

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Abstract

Nanotechnology is leading to the development in many field, of new materials and devices in many fields that demonstrate nanostructure-dependent properties. However, concern has been expressed that these same properties may present unique challenges to addressing potential health impact. Airborne particles associated with engineered nanomaterials are of particular concern, as they can readily enter the body through inhalation. Research into the potential occupational health risks associated with inhaling engineered nanostructured particles is just beginning. However, there is a large body of data on occupational and environmental aerosols, which is applicable to developing an initial assessment of potential risk and risk reduction strategies. Epidemiological and pathological studies of occupational and environmental exposures to airborne particles and fibers provide information on the aerosol-related lung diseases and conditions that have been observed in humans. Toxicological studies provide information on the specific disease mechanisms, dose–response relationships, and the particle characteristics that influence toxicity, including the size, surface area, chemistry or reactivity, solubility, and shape. Potential health risk will depend on the magnitude and nature of exposures to airborne nanostructured particles, and on the release, dispersion, transformation and control of materials in the workplace. Aerosol control methods have not been well-characterized for nanometer diameter particles, although theory and limited experimental data indicate that conventional ventilation, engineering control and filtration approaches should be applicable in many situations. Current information supports the development of preliminary guiding principles on working with engineered nanomaterials. However critical research questions remain to be answered before the potential health risk of airborne nanostructured particles in the workplace can be fully addressed.

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Introduction

Airborne particles are ubiquitous in the air we breathe, and have been an integral component of the earth's atmosphere for as long as generation mechanisms such as fires, volcanic emissions, sea spray and dust re-suspension have been in existence. Natural aerosol sources are estimated as accounting for between 65% and 95% of the global aerosol mass burden of all particle sizes (Baltensperger and Nyeki, 1998). Naturally occurring processes lead to particles being generated in the nanometer size range, including gas-to-particle conversion from volcanic emissions and aerosol emissions associated with trees and other plants (e.g., particle formation from terpenes). Anthropogenic sources, primarily involving combustion of fossil fuels, account for a significant proportion of nanometer–diameter aerosols in urban areas (e.g. Cass et al., 2000; Harrison et al., 2000), and many industrial processes, including welding, smelting and the use of diesel engines, lead to the production of airborne particles in the nanometer size range.

In response to the continual presence of airborne particles, human lungs have developed biological mechanisms for dealing with inhaled particles of all sizes (Parent, 1992; McClellan, 2000). However, these lung clearance and defense mechanisms have limits, and airborne particles from natural and anthropogenic sources have long been recognized as a potential health risk at sufficiently high concentrations and durations of exposure. The occupational health literature is replete with examples of respiratory hazards and studies of lung diseases associated with aerosol exposures in the workplace, and modern occupational health research on airborne particles and fibers dates back many decades.

Recent years have seen an increasing emphasis on the health impact of particles in the submicrometer and even nanometer size ranges in both the environment and the workplace. Events such as the London Smog episode of 1952 (Ministry of Health, 1954) have demonstrated the potentially severe health impact of inhaling fine aerosol particles and underpin recent epidemiology showing increased morbidity and mortality with exposure to particulate matter (PM) smaller than 10 μm (PM10) and 2.5 μm (PM2.5) in diameter (Dockery et al., 1993; Schwartz and Morris, 1995; Seaton et al., 1995; Wichmann and Peters, 2000; Pope et al., 2002). At the same time, research since the 1980s has been challenging our understanding of how nanometer–diameter particles impact the respiratory system and beyond (Donaldson et al., 2000; Oberdörster, 2000; Kreyling et al., 2002; Oberdörster et al., 2004). The significance of this research was initially seen in the context of occupational exposures to nanometer–diameter particles formed as by-products during processes such as welding, smelting and combustion. Although never formally defined, the term 'ultrafine particle' found increasing use as a descriptor of airborne particles smaller than 100 nm (Brown et al., 2003).

Research into the impact of occupational and environmental "ultrafine" particles has gained considerable attention in recent years due to the rapid development of nanotechnology – as predicted more than a decade ago:

> "Although at present ultrafine particles may not be of major importance at the workplace, this may change with increasing future applications and use of new-technology compounds" (Oberdörster et al., 1992).

In the 13 years since this was written, nanotechnology has more than fulfilled this prediction, with significant government, public and industry interest in the potential health and environmental impact of engineered nanomaterials being demonstrated (ETC Group, 2003; Hood, 2004; NSET, 2004; The Royal Society and The Royal Academy of Engineering, 2004).

Nanotechnology is a generic term encompassing the manipulation of matter at atomic and near-atomic length scales to produce new materials, structures and devices. Nanostructured materials, including nanometer–diameter particles or nanoparticles, are defined as having at least one dimension < 100 nm. Engineered nanomaterials typically possess unique properties (e.g., chemical, mechanical, electrical, optical, magnetic, biological), which make them desirable for commercial or medical applications. Although there are many routes to manipulating matter at the nanoscale, the production and use of nanometer–diameter particles has played and continues to play an

important role in nanotechnology (Choi et al., 2003; Friedlander and Pui, 2004). The fusion of new research findings on the health impact of particles in this size range, combined with the purposeful production of engineered particles with custom-made nanometer-scale sizes and structures, has served to elevate interest in the human health impact of nanotechnology – particularly in the workplace where these materials are produced and used (Maynard, 2004).

While occupational exposures to nanometer–diameter and nanometer-structured particles have been occurring for many years, and have been associated with lung diseases, the advent of nanotechnology producing and using new and exotic nanometer-structured materials raises many questions and concerns. Three questions in particular reflect current data and information gaps: What are the hazards associated with engineered nanomaterials (i.e., the inherent properties of the material that can cause harm)? Is there a health risk to workers from nanomaterials (which depends on the external exposure, internal dose, and biological response)? How can potential risks be minimized or eliminated? This review focuses on inhalation of airborne materials because inhalation has been the most common route of exposure to particulates in the workplace, and inhalation exposure is likely to continue to be important for nanomaterials. Dermal exposure is another potential route of exposure for nanoparticles (Tinkle et al., 2003), and more research is needed in this area. In this perspective, the current understanding on evaluating and managing inhalation exposure to airborne nanostructured materials is discussed in the broader context of occupational aerosols.

Historical perspective

Occupational illness has been associated with the inhalation of airborne particles since the earliest times, and remains a major cause of ill health within the workplace to this day (NIOSH, 2003; Maynard and Baron, 2004). In the 4th century BC, Hippocrates (c. 460–370 BCE) recorded details of occupational diseases associated with aerosols, including lead poisoning (Hunter, 1978; Rose, 1997), and Plinius Secundus (Pliny the Elder, 23–79) recognized the harmfulness of inhaling dust in the 1st century AD, noting the use of loose bladders wrapped round refiners' faces to prevent inhalation of 'fatal dust' (Plogg and Quinlan, 2002). However, it wasn't until the 15th and 16th centuries that a greater understanding of the relationships between aerosol exposure and occupational health began to emerge. The founders of modern occupational hygiene such as Paracelsus (1493–1541), Agricola (1495–1555) and Ramazzini (1633–1714) were clearly influenced by the incidence of ill health and death associated with mining and many other industries. Without exception, aerosols were acknowledged by these authors as presenting a major health hazard to workers in industrial environments. Ramazzini in particular documented many occupations where inhalation of "...very fine particles inimical to human beings..." was a problem (Ramazzini, 1964), including the inhalation of metal particles, gypsum, flour, stone dust and tobacco dust.

The industrial revolution of the late 19th and early 20th centuries introduced new and greater exposures to aerosols, and increasing awareness of the associated hazards. Mining was undertaken with increased intensity – particularly for coal – and exposure to soot, metal fumes and aerosols such as cotton dust increased markedly. Seminal research by the physician Alice Hamilton in the early 1900s laid the foundation for occupational hygiene in the USA (Hunter, 1978), and clearly linked aerosol exposure to ill health. At the same time, the work of researchers such as Tyndall, Aitken and Rayleigh provided the basis for modern aerosol science that would provide the means to understand, measure and control occupational exposures.

Although modern occupational hygiene has developed significantly from its roots, aerosols remain occupational respiratory hazards. Unlike gases or vapors, they pose a particularly complex hazard where dose and toxicity are associated with physical parameters as well as composition. Aerosol exposure assessment therefore needs to reflect the role of particle size and shape as well as chemistry. In the early 1900s, exposure to coal dust was evaluated by counting the number concentration of particles capable of reaching the gas exchange region of the lungs (Green and Watson, 1935; Walton and Vincent, 1998). The role of aerosol surface-area in determining health impact was also explored, and methods developed to allow appropriate exposure measurements

(Talbot, 1966, 1967). However, in the mid 1900's, research began to indicate that relatively simple measurements of mass concentration showed a close correlation with pulmonary disease in miners (Bedford and Warner, 1943). With the exception of fibrous aerosols, occupational aerosol exposure is now generally assessed with respect to mass concentration and bulk chemical composition (Maynard and Baron, 2004).

Lung dosimetry

When particles are inhaled, depending on their size, they may deposit in different regions of the respiratory tract, including the nasal, tracheobronchial, or alveolar (gas-exchange) region. Particles that reach the alveolar region may be phagocytosed (engulfed) by alveolar macrophage cells and cleared to the tracheobronchial region via the "mucociliary escalator," and then swallowed or expectorated (Parent, 1992; McClellan, 2002). Thus, the ingestion route of exposure also occurs when particles are inhaled. Inter-individual differences in deposition and clearance occur in the human population, and factors such as age, preexisting respiratory conditions, and exposure to other respiratory hazards (e.g., cigarette smoke), can influence the retention and susceptibility to airborne PM (ICRP, 1994).

Although many factors influence the potential health impact of inhaled particles, size and mobility play a key role in determining the probability of a particle entering the respiratory system, where it is most likely to deposit, and how it will eventually be cleared or removed. For anisotropic (non-spherical) particles, a single descriptor of 'diameter' is not a primary characteristic, but is determined by how it is defined and measured (Hinds, 1999).

Aerosol penetration into and deposition within the respiratory system has been studied and modeled extensively (ICRP, 1994; Martonen et al., 2005). Airborne particle aspiration depends on a number of parameters, including particle size, external air speed, orientation to the prevailing air movement direction, and minute ventilation. However, for external wind speeds of a few meters per second and lower, the probability of a particle entering the mouth or nose (termed inhalable particles) may be generalized as being around 100% for particles with aerodynamic diameters of a few micrometers and below, reducing to around 50% at 100 μm aerodynamic diameter (Vincent et al., 1990;

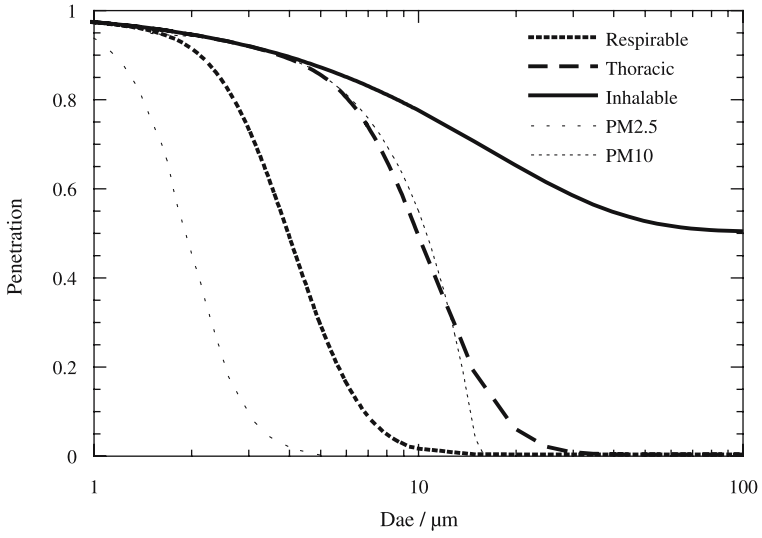

Figure 1. Standardized curves describing aerosol particle penetration probability into the respiratory system as a function of diameter. The inhalable curve describes particle penetraton into the respiratory system, while the thoracic curve described penetration beyond the upper airways and the respirable curve describes particle penetration to the gas-exchange region of the lungs (ISO, 1995). Environmental aerosol sampling conventions are also shown for comparison.

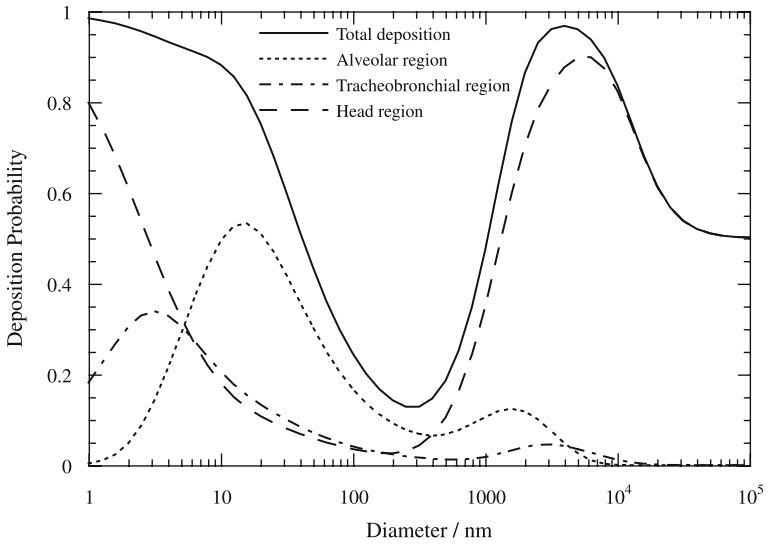

Figure 2. Modeled total particle deposition probability in the respiratory tract, and deposition probability in the alveolar region (ICRP, 1994). Deposition has been modeled assuming an adult breathing through their nose at 25 l/min (light exercise), and exposed to spherical particles with a density of 1000 kg/m^3.

ISO, 1995) (Figure 1). Particles smaller than 10 μm in diameter have a greater than 50% probability of penetrating beyond the head airways. While particles smaller than 10 μm aerodynamic diameter have some probability of reaching the gas exchange (alveolar) region of the lungs, there is at least a 50% probability for particles smaller than 4 μm aerodynamic diameter reaching this region (Lippmann, 1977; ISO, 1995; ICRP, 1994).

Inertial mechanisms dominate the behavior of larger particles entering the respiratory tract, leading to preferential deposition in the upper airways (Figure 2). At small particle diameters, inertia is secondary to Brownian diffusion in determining deposition, leading to particles penetrating deep into the lungs, and diffusing to the high lung surface area presented in the alveolar region. These competing deposition mechanisms lead to a minimum in deposition probability for particles between 100 nm and 1 μm in diameter. Particles smaller than a few tens of nanometers in diameter have an increasingly high coefficient of diffusion (which varies inversely with the square of particle diameter in the free molecular regime), leading to increasing deposition probability in the upper airways, before the particles are transported to the deep lung (Figure 2).

Particle deposition modeling indicates that up to 90% or more of the inhaled mass fraction of particles smaller than 100 nm will deposit in the human respiratory tract, with up to approximately 50% in the alveolar region (ICRP, 1994) (Figure 2). This model also predicts up to 99% particle deposition within the respiratory tract at 1 nm. The mass-fraction of nanometer–diameter particles depositing in the alveolar region of the lungs is greater than that for larger respirable particles by a factor of approximately 2–5 (ICRP, 1994), leading to proportionally high numbers of smaller particles at equivalent mass exposures. The fraction of depositing particles is higher with exercise (Jaques and Kim, 2000; Daigle et al., 2003) and among individuals with existing lung conditions including asthma and chronic obstructive pulmonary disease (COPD) (Brown et al., 2002; Chalupa et al., 2004). Studies have shown that inhaled particles, including fine and ultrafine particles, deposit preferentially at airway bifurcations and centers of lung acini (centriacinar region) (Churg and Vedal, 1996), and that the retained particle dose can be hundreds of times greater than the average dose in whole lungs (Balásházy and Hofmann, 2000). The airway bifurcations and centriacinar regions are also predominant sites for

lung injury, inflammation, and disease including COPD and lung cancer (Balásházy et al., 2003).

While deposition models (e.g., ICRP, 1994; CIIT and RIVM, 2002) account for particle size in predicting deposition within the major regions of the respiratory tract (nasopharyngeal, tracheobronchial, and alveolar), they do not currently describe the deposition in "hotspot" regions. Similarly, clearance and retention models (e.g. ICRP, 1994; Kuempel et al., 2001a, b) describe the particle mass transfer without specific allowance for particle size, although rodent studies have shown differences in the clearance and retention of inhaled nanoparticles compared to larger particles. These models are also limited in their descriptions of population variability and the factors influencing particle deposition and clearance (e.g., preexisting lung disease or conditions). These are important areas for further research in dosimetry modeling in order to better predict internal doses following exposure to nanoparticles.

Epidemiology and pathology studies

Although there are currently no studies of exposure and response to new engineered nanomaterials in humans, studies of humans exposed to other aerosols provide a context for evaluating the potential health hazard of exposure to nanometer–diameter particles in the workplace. Human studies are often limited in the data available to quantify the exposure levels or characterize the aerosol (e.g., particle size and composition). However, these studies provide valuable insight into the lung diseases and conditions that have been observed in humans exposed to airborne particles and fibers of many types and sizes (Parkes, 1994; Rom, 1998), and which may be relevant for nanostructured particles.

One of the most studied occupational groups has been coal miners, who have experienced elevated morbidity and morality from pulmonary fibrosis (coal workers' pneumoconiosis, CWP) and chronic obstructive lung diseases (Hurley et al., 1987; Marine et al., 1988; Attfield and Seixas, 1995; Kuempel et al., 1997, 2003). Both pulmonary fibrosis (silicosis) and lung cancer have been associated with exposure to respirable crystalline silica (Rice et al., 2001; Attfield and Costello, 2004), although lung cancer has not been associated with respirable coal mine dust exposure (Miller and Jacobsen, 1985; Kuempel et al., 1995; Morfeld et al., 1997). In workers exposed to titanium dioxide, one study found elevated lung cancer, but no exposure–response relationship (Boffetta et al., 2004), while another study found neither (Fryzek et al., 2003); exposure data were limited to the total dust (all sizes) or respirable dust fractions. Excess lung cancer mortality has been observed in hard metal workers exposed to tungsten carbide and cobalt; this excess mortality was related to exposure intensity and duration and remained statistically significant after adjustment for smoking and exposure to other carcinogens (Wild et al., 2000). Particle size information was not provided, but the excess lung cancer mortality was most strongly associated with exposure to the hard metal dust before sintering.

Aerosols containing nanometer–diameter metal particles (e.g., zinc oxide, tin) have been associated with an acute adverse response in welders known as metal fume fever (Antonini, 2003). Welding fume has also been associated with chronic bronchitis (Sferlazza and Beckett, 1991), and with elevated lung cancer in some studies but not others (reviewed in Antonini (2003)). Other aerosols containing a nanoparticle fraction include carbon black, which has been associated with adverse respiratory symptoms and decrements in lung function (Gardiner et al., 2001), and with elevated lung cancer mortality among workers (but not associated with cumulative exposure) (Sorahan et al., 2001). Beryllium has been associated with acute pneumonitis, chronic beryllium disease (CBD), and lung cancer (Kreiss et al., 1997); of particular interest is the possible mechanism for CBD sensitization via dermal exposure (Tinkle et al., 2003). Diesel exhaust particulate has been associated with acute pulmonary and systemic inflammation in healthy human volunteers (without lung function decrement) (Salvi et al., 1999) and with elevated lung cancer in some studies of workers (Steenland et al., 1998; Garshick et al., 2004) but not in others.

Exposure to airborne asbestos fibers has long been associated with an increased risks of both nonmalignant (asbestosis) and malignant lung diseases (lung cancer and mesothelioma) (Doll, 1955; Peto et al., 1977). More recently, nylon flocking has emerged as a newly recognized

occupational respiratory hazard, associated with interstitial pneumonitis, lung function decrements, and adverse respiratory symptoms in workers (Washko et al., 2000; Daroowalla et al., 2005).

Pathological studies in humans have reported abnormal structural changes in the small airways (airway remodeling), along with the retention of ultrafine and fine particles in lung tissue, in both agriculture workers (Pinkerton et al., 2000) and residents of Mexico City, a region of chronically high PM (the 3-year mean PM10 was 66 $\mu g/m^3$) (Churg et al., 2003). In the agricultural workers, the carbonaceous and mineral dust was found to be retained predominantly in the centers of lung acini and was associated with the degree of fibrosis (Pinkerton et al., 2000). In the Mexico City residents who were lifelong nonsmokers, the particles retained in bronchial airway walls were fine aggregated particles (~0.3–0.5 μm) which contained individual ultrafine particles (~0.04–0.07 μm) in bronchial airway walls. Airway remodeling, which involves fibrotic thickening of the airway walls, has been hypothesized as contributing to the development of chronic obstructive pulmonary disease (Churg et al., 2003). Evidence for extrapulmonary translocation of respirable-size particles has been observed in coal miners – black pigment in the liver and spleen was associated with years in mining and severity of CWP, but was not associated with pathological tissue response in the liver and spleen (LeFevre et al., 1982).

Toxicological studies

Many of the biological mechanisms involved in particle-related lung diseases (e.g., oxidative stress, inflammation, production of cytokines, chemokines, and cell growth factors) (Mossman and Churg, 1998; Castranova, 2000) also appear to be involved in lung responses to nanometer–diameter particles (Donaldson et al., 1998; Donaldson and Stone, 2003; Oberdörster et al., 2005). Much of our understanding about the key factors that influence the biological reactivity and toxicity of airborne PM has come from toxicological studies. These factors – which include size, surface area, surface chemistry, solubility, and shape – influence both the disposition of particles in the lungs and the biological responses that are elicited. Particles that remain in the lungs may cause inflammation, tissue damage, and disease (Donaldson et al., 1998). Particles that escape the lungs and enter the blood circulation may cause endothelial cell injury (of the blood vessels) and prothrombotic effects (blood clot formation) (Nemmar et al., 2004). Recent studies have indicated that particles depositing in the nasal region may be transported to the olfactory bulb via the olfactory nerves (Oberdörster et al., 2004), presenting a previously overlooked exposure route. Discussions are continuing about the key chemical and physical properties that influence the toxicity of inhaled nanometer–diameter particles (Oberdörster and Utell, 2002; Donaldson et al., 2004; Warheit, 2004).

Size

The particle size has been shown to influence both the disposition (fate) and the biological responses in the lungs (Ferin and Oberdörster, 1992; Oberdörster et al., 1992). In rats, the smaller ultrafine particles (12 and 20 μm) were found to penetrate the alveolar epithelial lining and enter the lung interstitium to a greater extent than an equal mass of larger respirable particles (>200 μm) (24 h following intratracheal instillation), and that proportion increased with increasing particle dose (as mass or surface area) (Oberdörster et al., 1992). Much greater inflammation (measured by neutrophil cells and protein in lavage fluid) was observed for the ultrafine particles compared to the larger respirable particles. Similar results have been observed for other metals, including aluminum oxide (Al_2O_3) (Ferin et al., 1991), gallium oxide (Ga_2O_3) (Webb et al., 1986; Wolff et al., 1988), cobalt (Zhang et al., 2000), and nickel (Zhang et al., 2003).

The size of nanometer–diameter particles may also allow them to more readily enter cells and cellular organelles. In a study of concentrated particles from air pollution, in human bronchial epithelial cells and mouse alveolar macrophages, the ultrafine fraction (<100 nm) was found to penetrate into cells and localize in mitochondria, causing oxidative damage to mitochondrial membranes (Li et al., 2003). Ultrafine particulate including carbon black (12 nm), elemental carbon (90 nm), and diesel exhaust particulate (120 nm; a

standard reference material; presumably agglomerated) caused various measures of cytoskeletal dysfunction including impaired phagocytosis (approximately 50% of controls), inhibited cell proliferation, and decreased cell viability in primary alveolar macrophages from dogs and a mouse alveolar macrophage cell line (in 24 h) (Möller et al., 2002).

There is some evidence that nanometer–diameter particles can pass from the lungs into the bloodstream and might present a systemic health hazard. Inhaled ultrafine carbon (^{13}C) particles (approximately 25 nm diameter) were shown to rapidly clear from rat lungs (within 24 h) and translocate to other organs including liver and spleen (Oberdörster et al., 2002). Inhaled ultrafine elemental silver particles in rats were rapidly removed from the lungs to the blood circulation (within 30 min), but when the same type of particles was instilled into rat lungs, some agglomerates remained for at least 7 days (Takenaka et al., 2001). Nemmar et al. (2001, 2002) reported translocation of radiolabeled ultrafine carbon particles from the lungs into the blood, in studies in both hamsters and humans (although there is some question whether the radiolabel remained attached to the carbon particles). In contrast, iridium particles remained primarily in rat lungs after one week (less than 1% was translocated to extrapulmonary organs; yet, of the particles that did translocate, nearly 10 times more were the 15 nm particles than the 80-nm particles) (Kreyling et al., 2002). The extent of particle aggregation and interactions with proteins are factors that have been hypothesized to influence the translocation of inhaled nanometer–diameter particles (Kreyling et al., 2002).

Surface area

The dose of particles, expressed as particle surface area, has been shown in a number of studies to be closely associated with lung responses including inflammation and tissue damage in rat lungs (Oberdörster et al., 1992, 1994b; Lison et al., 1997; Tran et al., 1999, 2000; Brown et al., 2001; Duffin et al., 2002). These studies have shown that despite the varying particle compositions, sizes and morphologies, the aerosol surface area dose–response relationship appears to be remarkably similar for poorly soluble, low toxicity (PSLT) particles. Studies in rats have shown that at lung doses of

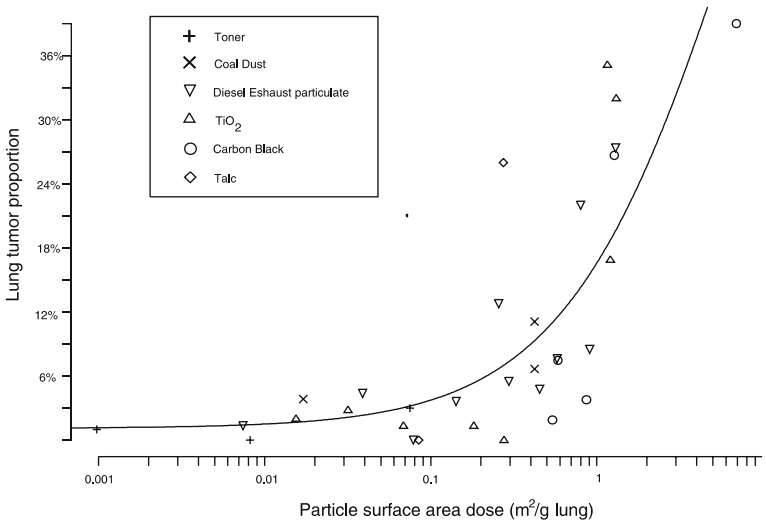

Figure 3. Relationship between TiO_2 surface area dose in the lungs of rats after chronic inhalation to various types of poorly soluble low toxicity (PSLT) particles and tumor proportion (all tumors including keratinizing squamous cell cysts). *Data from*: Toner (Muhle et al., 1991); coal dust (Martin et al., 1977); diesel exhaust particulate (Mauderly et al., 1987; Lewis et al., 1989; Heinrich et al., 1995; Nikula et al., 1995); titanium dioxide (TiO_2) (Lee et al., 1985; Muhle et al., 1991; Heinrich et al., 1995); carbon black (Heinrich et al., 1995; Nikula et al., 1995); talc (NTP, 1993). Similar plots have been published by Oberdörster and Yu (1990), Driscoll (1996) and Miller (1999).

PSLT particles that impair (overload) lung clearance (Morrow, 1994), the lung responses include persistent inflammation, tissue damage, fibrosis, and lung cancer. Interestingly, ultrafine particles were recognized early as not fitting the volumetric particle overload hypothesis since clearance was reduced at lower doses of ultrafines than expected (Morrow et al., 1991). More recently, inhibition of clearance has been shown to be better predicted by particle surface area dose (Tran et al., 1999). Particle surface area has also been shown to be a better metric than mass for predicting lung tumors in rats chronically exposed by inhalation to various fine or ultrafine PSLT (Figure 3). Although diesel exhaust PM is not strictly a PSLT because of the adsorbed organic substances, the rat lung tumor response is consistent with that of the carbon core as a PSLT particle (Heinrich et al., 1995; Nikula et al., 1995). These relationships have been observed with particle surface area dose, even though many of these particles likely exist as agglomerates rather than individual nanometer–diameter particles (Maynard, 2002).

Surface chemistry

The surface reactivity of aerosols has long been known to be a key factor influencing the toxicity of inhaled particles. Insoluble particles that are chemically active such as crystalline silica, remain markedly more toxic than other insoluble materials, even when normalized for surface area. Oberdörster et al. (1994b) and Duffin et al. (2002) showed that pulmonary inflammation was much higher in rats exposed to crystalline silica than in those exposed to fine or ultrafine TiO_2 particles (by inhalation or intratracheal instillation), even when dose was expressed as particle surface area. Crystalline silica is highly reactive with biological membranes, by a mechanism involving hydroxyl radical-mediated lipid peroxidation (Castranova, 1998), which can result in cell death. Radicals may be present on the particle surfaces, and reactive oxygen or nitrogen species may also be released from phagocytic cells that engulf particles in the lungs. The presence of excess oxidants may activate the production of inflammatory cytokines, leading to the recruitment of neutrophils (inflammatory cells) into the lung air spaces and the production of cell proliferation factors; oxidants can also damage DNA (Fubini, 1998; Castranova and Vallyathan, 2000). Duffin et al. (2002) showed that by modifying the surface of the quartz (e.g., with aluminum lactate), the inflammation response was reduced to that observed for the particles with relatively low toxicity (TiO_2, carbon black, latex).

Among ultrafine particles (approximately 20 nm diameter), differences in pulmonary inflammation and cytotoxicty (observed in rats exposed by intratracheal instillation) were associated with the particle surface free radical activity – ultrafine nickel was more toxic than ultrafine cobalt (or than respirable crystalline silica), while ultrafine TiO_2 was the least toxic in that study (Zhang et al., 1998). In another rat instillation study, the inflammatory response to four different types of ultrafine particles (carbon black, cobalt, nickel, and titanium dioxide) was consistent with their measured free radical generation (Dick et al., 2003). A recent study has shown that surface modification of engineered carbon-60 fullerene (C_{60}) reduced its cytotoxocity in a cell viability assay, which was suggested to occur via oxygen radical generation (Sayes et al., 2004). While the underivatized (unmodified) form was highly toxic to a human cell line (at 20 ppb), and had been shown previously to cause oxidative damage in the brains of fish (Oberdörster, 2004), modification of the molecular structure by hydroxylation reduced the cytotoxicity by several orders of magnitude (Sayes et al., 2004).

The influence of both particle surface area and composition on toxicity is illustrated in Figures 4 and 5. Figure 4 shows the relationship between pulmonary inflammation and the mass dose of fine or nanometer–diameter PSLT particles (titanium dioxide and barium sulfate) or toxic particles (crystalline silica). On a mass basis, nanometer–diameter titanium dioxide is more inflammogenic than fine PSLT, but still less inflammogenic than fine crystalline silica. Figure 5 shows that when the same data are plotted using particle surface area dose, the fine and ultrafine PSLT show a consistent dose–response, while the crystalline silica is still more inflammogenic per unit of surface area dose.

Nanometer–diameter polytetrafluoroethene (PTFE) particles generated through thermal degradation above 425°C, can form a highly reactive and toxic aerosol. Rats that inhaled discrete 26 nm diameter PTFE particles at relatively low mass concentration ($<60\ \mu m/m^3$) died of hemorrhagic pulmonary inflammation within 10–30 min of

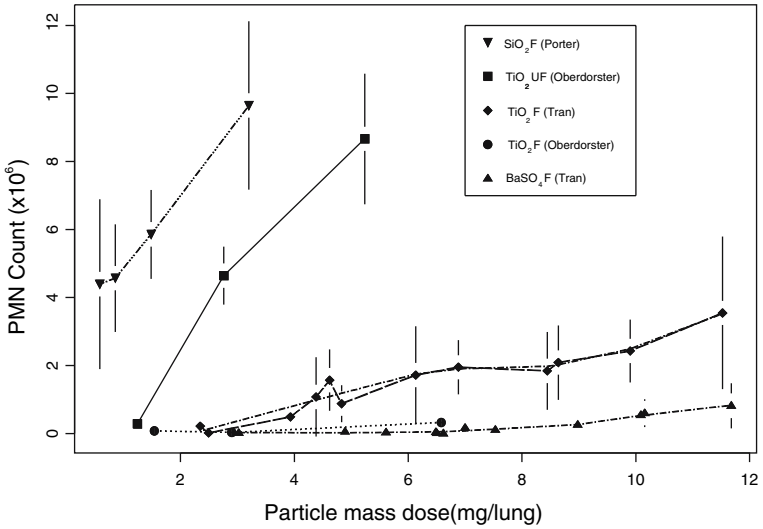

Figure 4. Pulmonary inflammation (PMN count) of high toxicity dust (crystalline silica) particles compared to low toxicity dust (TiO_2 and $BaSO_4$) of both fine and nanometer–diameter particles, based on particle *mass* dose in rat lungs. Data from: Porter et al. (1999), Oberdörster et al. (1994a), Tran et al. (1999). Particle size: F (fine); UF (ultrafine).

exposure (Oberdörster et al., 1995). The authors suggested that the PTFE particles had caused severe oxidative stress, and they noted that when the rats were exposed to aged fumes (which formed aggregates with median diameters slightly greater than 100 nm, and which likely had fewer reactive surface groups), the toxicity was considerably reduced (and no rats died). Some early studies reported pulmonary edema in individuals inhaling PTFE pyrolysis products (Evans, 1973; Brubaker, 1977).

The polycationic structure of polymeric paint compounds (i.e., multiple positive charges on their nitrogen atoms at physiological pH) was found to

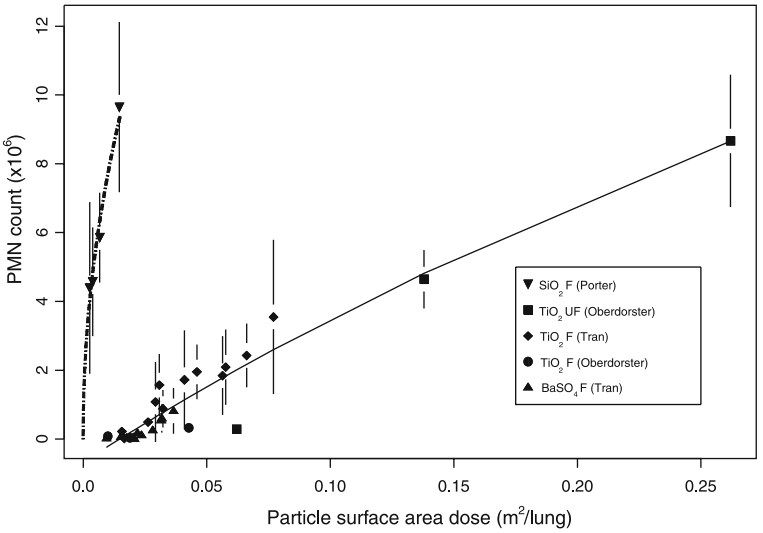

Figure 5. Pulmonary inflammation (PMN count) of high toxicity dust (crystalline silica) particles compared to low toxicity dust (TiO_2 and $BaSO_4$) of both fine and ultrafine size – based on particle *surface area* dose in rat lungs. Data from: Porter et al. (1999), Oberdörster (1994a), Tran (1999). Particle size: F (fine); UF (ultrafine).

be a key determinant in the *in vitro* cytotoxicity of these compounds in human or rat lung cells (pneumocytes and alveolar macrophages) (Hoet et al., 2001). These polymeric materials, which previously had been thought to be of low toxicity due to their low reactivity compared to the constituent monomers, are thought to be the cause of severe occupational lung disease (bronchiolitis obliterans organizing pneumonia) in textile paint sprayers (Camus and Nemery, 1998).

Solubility

A number of studies have shown that the solubility of inhaled particles and fibers influences their toxicity. Poorly soluble substances retained in the lungs can cause oxidative stress, either directly from free radicals on their surfaces or indirectly by triggering the influx of defensive cells into the lungs, leading to inflammation, fibrosis, or cancer (Castranova, 1998; Donaldson et al., 1998; Dreher, 2000; Stone et al., 2000; Zhang and Kusaka, 2000; Brown et al., 2001; Donaldson et al., 2001; Dick et al., 2003; MacNee and Donaldson, 2003). Ultrafine particles have been shown to be more potent in causing these effects than an equal mass of larger particles of the same composition (see "Surface Area" section).

Both the water-soluble and insoluble fractions of welding fume (manual metal arc with flux-covered stainless steel electrode) were cytotoxic and inflammogenic, although different lung cells were induced by each fraction (neutrophils: insoluble; eosinophils: soluble) (Antonini et al. (2003). Kodavanti et al. (1998) found that the adverse responses to residual oil fly ash (ROFA) in rat lungs were associated with specific water-leachable metals in the ROFA; increased protein and lactate dehydrogenase (indicating tissue damage) were associated with water-leachable total metal, nickel (Ni), iron (Fe) and sulfate, while pulmonary inflammation was associated with water-leachable vanadium (V). In rats administered a single dose of solubilized arsenic trioxide (As_2O_3) (by intratracheal instillation), transient increases were seen in total protein and albumin (suggesting lesions in the alveolar-capillary barrier), while the effects from crystalline silica were persistent and progressive (Lasfargues et al., 1995). A mixed exposure to tungsten carbide and cobalt (WC-Co) caused acute alveolitis (after a single intratracheal dose) and fibrosis (after repeated doses), while those effects were not observed in rats exposed to either metal alone (Lasfargues et al., 1995) (see Epidemiology and Pathology Studies section for WC-Co study in workers). In a chronic inhalation study in rats, poorly soluble crystalline nickel subsulfide (Ni_3S_2) and nickel oxide (NiO) caused exposure-related increases in alveolar/bronchiolar neoplasms and adrenal medulla neoplasms, while no excess neoplasms were observed in the rats exposed to the water-soluble compound nickel sulfate hexahydrate ($NiSO_3 \cdot 6H_2O$) (Dunnick et al., 1995). A mechanism has been proposed whereby the poorly soluble nickel compounds are able to enter cells via phagocytosis, and the Ni ions released inside vacuoles can enter the nucleus and interact with chromatin proteins (Costa et al., 1994).

The effect of decreasing particle size to the nanosize range would be expected to increase the solubility. Other factors influencing solubility, as observed with various cobalt compounds, include dilution (partially soluble materials were more soluble with increased dilution) and pH (some compounds were less soluble in a neutral lung fluid surrogate compared to the more acidic lysosome fluid surrogate) (Stopford et al., 2003).

Shape

Most studies on nanometer–diameter particles and health have focused on approximately isotropic primary particles, and agglomerates/aggregates of these particles. However exposure to anisotropic particles such as fibers (e.g., asbestos) has long been associated with increased risk of fibrosis, lung cancer, and mesothelioma (Doll, 1955; Peto et al., 1977). This raises additional concerns over the role of particle morphology when considering some complex nanostructured materials. Nanometer–diameter tubular or fibrous structures, such as carbon nanotubes, represent a unique class of nanomaterial. As early as 1992, caution was raised over the potential health risk of such materials, in response to their proposed application in reinforced polymer composites (Calvert, 1992; Coles, 1992). Specific attention has been paid to single walled carbon nanotubes (SWCNT), which are characterized by a single graphene sheet of carbon atoms arranged in a tube-structure approximately 1.4 nm in diameter. When formed in the gas-phase, SWCNT are usually produced using

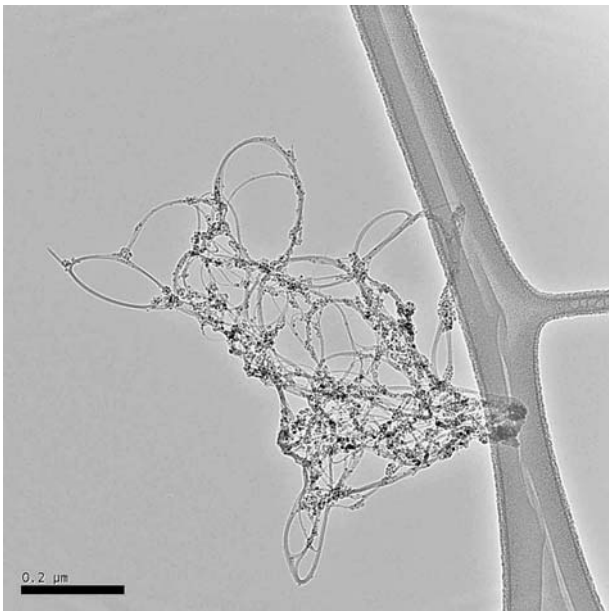

Figure 6. Transmission electron micrograph of a 150 nm mobility diameter aerosol particle released from unprocessed single walled carbon nanotube material.

nanometer–diameter transition metal catalyst particles (Sinnott and Andrews, 2001), and the resulting unprocessed material is a complex aggregate of SWCNT ropes (bundles of SWCNT), catalyst particles and non-tubular carbonaceous material. Even when purified, airborne particles of SWCNT have a complex convoluted morphology that is unique to the material (Figure 6).

Only a small number of *in vitro* and *in vivo* toxicity studies have been carried out using SWCNT to date (Huckzko and Lange, 2001; Huckzko et al., 2001; Shvedova et al., 2003; Lam et al., 2004; Warheit et al., 2004). The experimental design of the first two studies (*in vitro*) has been questioned (Warheit et al., 2004). In a study in mice, three different sources of SWCNT, with varying catalyst metal content, were found to produce dose-dependent granulomatous lesions and inflammation in mice exposed by intratracheal instillation to 0.1 and 0.5 mg of material and followed for 7 or 90 days (Lam et al., 2004). These lung lesions appeared to be progressive, with worse lesions generally seen at 90 days than at 7 days. The nickel-containing SWCNT was highly toxic and caused 50% mortality within 7 days at the high dose (Lam et al., 2004). The authors noted that SWCNT is more toxic than carbon black and can be more toxic than quartz on a mass basis. In another instillation study, in rats administered 1 and 5 mg/kg of SWCNT, 15% mortality occurred within 24 h – which was attributed to airway blockage by the SWCNT material (Warheit et al., 2004). In the rats that survived, multifocal granulomas were observed but without dose-dependence or persistent inflammation, although the high dose in this study (Warheit et al., 2004) was comparable to the low dose in Lam et al. (2004) (approximately 0.1 mg, after adjusting for mouse weight). (Shvedova et al., 2003) observed that in cell cultures of human keratinocytes, unpurified SWCT (containing 30% iron by mass) produced oxidative stress, cellular toxicity, and loss of cell viability. Treatment with a metal chelator suppressed the free radicals, suggesting that a Fenton-like (iron-requiring) reaction may be involved in oxidant generation and toxicity (Shvedova et al., 2003). In a recently published study of multi-walled carbon nanotubes (MWCNT), these structures (up to 3.6 μm in length) were found to penetrate into human epidermal keratinocytes (skin cell cultures) and to elicit production of an inflammatory cytokine (interleukin-8) (Monteiro-Riviere et al., 2005). Iron was not detected in these MWCNT preparations (Monteiro-Riviere et al., 2005).

Health-based aerosol particle definitions

At this point, it is useful to discuss in more depth those characteristics of nanotechnology-related particles that may be biologically relevant, and how these in turn may contribute to an appropriate health-related nomenclature. Nanotechnology typically involves the creation and use of sub-100 nm structures, and the exploitation of the unique properties associated with these structures. A wide range of nanostructured materials are formed as powders, suspensions or solutions that are comprised of primary particles with diameters smaller than 100 nm. Consequently, there has been a tendency to discuss airborne exposure to 'nanoparticles' or 'ultrafine particles' in terms of discrete sub-100 nm diameter particles. However, the unique properties of nanostructured materials are not confined to discrete nanometer–diameter particles. Aerosol particles of single walled carbon nanotubes such as those shown in Figure 6 demonstrate this point elegantly. With a particle diameter close to 1 μm in diameter, it is respirable and has a complex structure at a scale of just a few nanometers, which may be biologically accessible and may influence toxicity.

In the context of health risk, it is necessary to consider whether the nanostructure of a material leads to a specific or enhanced biological response, and whether the material can interact with the body in such a way that the nanostructure is bioavailable. Under these criteria, the size of discrete particles only becomes important where biological activity is associated with individual particles, and where size governs deposition location in the respiratory system and subsequent translocation. If particle nanostructure rather than diameter is the primary driver behind biological response, distinctions in terms of 'nanoparticles' or 'ultrafine particles' become meaningless. A viable alternative is the term 'nanostructured particle', describing particles with a biologically accessible structure on a nanoscale that leads to a high specific surface-area and/or unique properties associated with the structure. While such a definition is inclusive of sub-100 nm diameter discrete particles, it is broad enough to encompass all nanotechnology-related aerosols that may present a previously unrecognized health hazard. As further data on particle translocation becomes available, additional particle size-based definitions will most likely be necessary to describe transport to target organs and subsequent biological response.

A more complex definition that needs to be addressed is that of aerosol surface area. While toxicological studies show surface area is a good indicator of inflammogenic and tumorigenic responses to insoluble particles, a precise definition of 'biologically active' or 'biologically available' surface area has yet to be agreed on. Nanostructured particle surfaces can be fractal-like, meaning that measured surface area, and most likely biologically available surface area, is a function of length-scale (e.g. surface area measured at a resolution of 1 Å may differ substantially from surface area measured at a resolution of 10 nm). In addition, definitions of surface area may include or exclude internal voids (porosity). As progress is made towards understanding the relationship between biological mechanisms and aerosol surface area, and appropriate surface area characterization techniques are developed, a clear understanding of the definition and nature of biologically relevant surface area will be essential.

Nanostructured particle generation, dispersion and transformation

Exposure to engineered nanostructured particles in the workplace will depend on the release of particles from processes into the air, and subsequent dispersion within the workplace (Luther, 2004). In addition, transformations between generation and inhalation affecting particle size, shape, surface area and chemistry may critically influence the significance of subsequent exposures. Release of nanostructured particles from powders and direct-emission of nano-aerosols into the air will clearly present potential sources. However, aerosolization of nanostructured particle suspensions and solutions will also enable nanomaterials to enter the respiratory tract through inhalation. The UK Health and Safety Executive has published a comprehensive review of production processes involving nanostructured particles (Aitken et al., 2004).

Processes leading to direct nanostructured particle release into the air will most likely involve gas phase synthesis (Kruis et al., 1998; Swihart, 2003). In many cases, such processes will be enclosed to maintain the conditions required for synthesis, or to contain the synthesized material. In such cases,

emissions will most likely be associated with unintentional leaks. In the case of more open production systems, there will be the potential for direct nanostructured particle emissions into the air if appropriate emission control approaches are not adopted. Established gas phase nanostructured particle synthesis methods such as high specific surface-area carbon black production and fumed metal oxide production use relatively closed systems until the product is reduced to an easily handlable form. Although unintended leaks within such production routes always present a potential emission source, re-suspension of the product from the powder phase is more likely to be of concern.

Material re-suspension to form an aerosol of nanostructured particles may occur during maintenance on production systems or handling of dry nanopowders. The propensity for a powder to form an aerosol when agitated is governed by many factors, and is currently not clearly understood. Research into the 'dustiness' of powders has led to test methods designed to evaluate the release of inhalable and respirable particles (Heitbrink et al., 1992; HSE, 1996). These methods may not be applicable to nanostructured materials without further development, however. Maynard et al. (2004) have qualitatively evaluated the release of aerosol particles from SWCNT during agitation, and particle number concentration release rates have been shown to be lower than those from nanostructured aluminum oxide powder (Baron et al., 2003). Field studies have shown that, on a mass basis, release of unprocessed single walled carbon nanotube aerosols is relatively low when the material is handled (Maynard et al., 2004). Measurements made while material was removed from reaction vessels and transferred between containers indicated airborne concentrations to be less than 50 $\mu g/m^3$. Real-time measurements of number concentration between 10 nm and approximately 1 μm did not indicate increases in number concentration exposure while the material was being handled. Measurements of aerosol emissions while bagging carbon black have shown PM10 mass concentrations were up to 20 times higher than ambient concentrations, with most particles having diameters larger than approximately 400 nm, while the ultrafine particles ($<$100 nm) were attributed to emissions sources rather than to carbon black (Kuhlbusch et al., 2004).

Aerosolization of nanomaterial solutions and suspensions is unlikely to lead to discrete nanometer–diameter particles unless the solution/suspension is extremely dilute, or a mechanism such as electrospray is involved. However, if the droplets resulting from aerosolization are inhalable, they will lead to nanomaterial delivery to the respiratory system, and if they are less than 4 μm in diameter there will be greater than 50% probability nanomaterial penetrating to the lungs (ISO, 1995). The size of droplets released into the air will depend on the generation process. Currently, there is no published information on exposure to aerosols of engineered nanomaterial suspensions or solutions, and without process-specific information, it is difficult to speculate on the likelihood of generating respirable droplets. However, the generation of aerosols through nebulization (Smythe et al., 2004) and the formation of metal working fluid aerosols during machining (Piacitelli et al., 2001), leading to respirable droplets, demonstrates the possibility of creating respirable liquid aerosols containing nanomaterials under appropriate conditions.

Dispersion following generation will depend on many factors specific to the environment into which an aerosol is released. The dynamics of nanometer–diameter particle behavior suggest that they will follow air-flows in general and not be influenced by mass and inertia-related mechanisms such as settling and inertial deposition. However, particle motion under external fields such as electrophoresis, magnetophoresis and thermophoresis may lead to deviation from air-flows. Electrical mobility of particles increases rapidly with decreasing diameter and increasing charge, although the probability of a particle holding charge decreases with decreasing diameter. Particles smaller than 10 nm have less than 0.7% probability of being charged in an aerosol at Boltzmann charge-equilibrium (Hinds, 1999). Thermophoresis is generally independent of particle diameter below approximately 100 nm (Talbot et al., 1980). Little is known of the importance of magnetophoresis, although it may be speculated that the presence of strong magnetic fields will influence the behavior of magnetic particles in some cases, including enhanced agglomeration (Kumar and Biswas, 2005). Each of these motive forces will influence aerosol concentration and

deposition when sufficient in magnitude to dominate the behavior of susceptible particles.

Diffusophoresis is unlikely to lead to nanostructured particles deviating significantly from gas flow streamlines. Even at 1 nm, the diffusion coefficient of airborne particles is less than a twentieth of that for air. Diffusion does affect particle-particle collisions and coagulation however (or coalescence if the particles are liquid), resulting in changes in particle size and morphology. Coagulation rate depends on the square of concentration, and thus dominates behavior at high concentrations but is negligible at low concentrations. Simple estimates of variations in aerosol number concentration resulting from coagulation (assuming no growth following collisions) show that a 50% reduction in concentration is expected within 20 s at concentrations of 10^{14} particles/m^3, and within 55 h at concentrations of 10^{10} particles/m^3 (Figure 7). Preining (1998) has calculated that number concentration half life for 10 nm diameter particles is 8.1 days at a mass concentration of 1 ng/m^3, 11.7 min at 1 μg/m^3 and 0.7 s at 1 mg/m^3. As a rule of thumb, nanometer–diameter particle concentrations below 10^{12} particles/m^3 (50% number concentration reduction in 33 min) can be assumed to be relatively stable in an occupational environment.

Coagulation alters both the size and structure of particles, thus affecting their potential health impact. Atmospheric nanometer–diameter particles typically grow to modal diameters between 100 and 300 nm (Whitby, 1978), representing a size range where further coagulation is quenched by decreasing number concentration and increasing particle size, and removal rates through mass-driven mechanisms such as settling are low. In occupational settings this modal diameter will be influenced by aerosol generation rates and residence times, and may extend beyond 1 μm in some circumstances. However, it is likely that in cases where aerosols are generated at concentrations above 10^{12} particles/m^3 and are not diluted significantly for some minutes, aerosols will be dominated by particles within this so-called accumulation mode.

Solid nanometer–diameter particles form fractal-like diffusion-limited agglomerates with fractal dimensions of typically between 1.75 and 2.5, depending on whether morphology is dominated by particle–cluster agglomeration or cluster–cluster agglomeration (Baron et al., 2001). Open-structured agglomerates with fractal-dimensions below two have specific surface-areas close to that of the constituent particles (Rogak et al., 1993). Thus if toxicity is driven by surface characteristics,

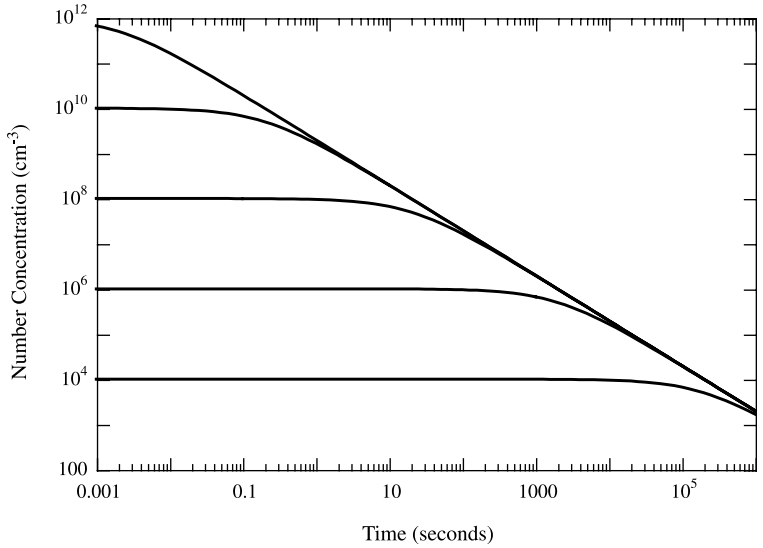

Figure 7. Estimated reductions in nanometer–diameter aerosol particle concentration with time, for a range of initial number concentrations (after Hinds (1999)). Monodisperse aerosol coagulation is been assumed.

it is anticipated that diffusion-limited coagulation will not have a significant impact on the hazard presented by airborne nanometer–diameter particles. However, deposition probability in the respiratory tract may vary considerably with coagulation as particle size varies (Figure 2).

Changes in particle diameter through agglomeration will influence translocation probability following deposition, although quantitative data on translocation as a function of particle size and chemistry are not yet sufficient to estimate the extent to which agglomeration will affect dose to organs beyond the respiratory system. It is also currently unknown to what extent agglomerates will de-agglomerate into smaller particles following deposition. Preliminary research has indicated that TiO_2 particles with a primary diameter of 25 nm generated as a fume, dispersed in simulated lung fluid as agglomerates with a modal diameter of approximately 100 nm (Maynard, 2002). However, a study of PM2.5 particles in lung lining fluid has suggested particle aggregation rather than de-agglomeration in the lungs (Kendall et al., 2002).

A final aspect of transformation between generation and inhalation is how the chemistry – and in particular the surface chemistry – of particles is altered. Particle exposure to gases and vapors will lead to adsorption and possible chemical reactions (oxidation being a clear transformation leading to a surface oxide layer in some cases). Exposure to light of specific wavelengths may lead to photoactivation and an alteration of surface chemistry; active sites on particle surfaces may be passivated with time, or coated or modified surfaces may wear, through various processes under the general umbrella of ''aerosol aging.''

Exposure measurement and characterization

Although current toxicity data support the hypothesis that surface-area and particle size are more significant physical parameters than mass concentration alone in determining health risk following nanostructured particle inhalation, the evidence is not yet sufficient to identify a clear general basis for exposure measurement and characterization. Appropriate methods will depend to a large degree on the context in which measurements are made. Toxicity studies require as complete a characterization of exposures as is practical, including measurement of parameters likely to be of significance such as aerosol surface-area and size distribution, and detailed characterization of particle morphology and surface chemistry before and after deposition. Measurements for assessing emissions, control efficacy and human exposure will follow a different set of criteria. In particular, *in situ* exposure monitoring frequently requires the measurement techniques to be robust, compact, inexpensive and relevant to appropriate exposure standards.

Mass concentration measurements offer continuity with historic and current monitoring approaches, but are relatively insensitive to nanometer–diameter particles. However, they may offer a bridge between established and new exposure monitoring approaches if the necessary sensitivity and appropriate particle size selectivity is achievable. If particle number or surface-area is a more relevant exposure metric, it may be possible to use mass concentration as a surrogate measurement where information on particle size distribution or aerosol specific surface-area is known.

Aerosol number concentration is relatively easy to measure above 10 nm using Condensation Particle Counters (CPCs), and may be extended to particles as small as 3 nm in diameter with relative ease (Cheng, 2001). Number concentration measurements are generally not size-specific though, unless made with an appropriate pre-separator for a specific particle size range. Consequently, it is difficult to distinguish between different sources of process-related aerosols, or between process and background aerosols. Kuhlbusch et al. (2004) found number concentration measurements in carbon black production facilities were frequently dominated by other aerosol sources, leading to difficulties in monitoring process-specific emissions using number alone. Despite this drawback, the use of number concentration measurements has been proposed for crude identification of nanometer aerosol emission sources in workplaces by carrying out measurements close to potential or suspected sources (Brouwer et al., 2004).

Published toxicological data support measuring insoluble aerosol exposure against surface-area in cases where surface-area and surface activity are more important than discrete particle size. Available methods to measure aerosol surface-area are

somewhat limited though. The Brunaeur, Emmett and Teller (BET) method of determining surface-area remains the standard measurement method for powders (Brunauer et al., 1938), and has been used for aerosol surface-area determination with some success (Lison et al., 1997). However, in addition to being an off-line technique, there is little information on how aerosol collection processes influence BET measurements, or the relationship between BET-derived particulate surface area and biologically relevant surface area. A second widely used method for determining particle and aerosol surface-area is Transmission Electron Microscopy (TEM). Through the use of image processing, the projected area of sampled particles can be determined with relative ease. Once again though, this is an off-line technique, and the results may not reflect the three-dimensional nature of analyzed particles.

A number of on-line methods are available for estimating aerosol surface-area. The most intuitive perhaps is derivation of surface-area from measured aerosol size distribution. The association between particle mobility diameter and surface-area in the free molecular regime is well established (e.g., Rogak et al., 1993; e.g., Ku and Maynard, 2005), allowing surface-area to be estimated reasonably well from size distributions with modal diameters below approximately 100 nm. For compact isotropic particles, size distributions extending from the free molecular to continuum gas regimes can in principle be used to estimate surface-area. In order to characterize aerosols with modal diameters of a few hundred nanometers and above, sizing techniques such as mobility analysis need to be coupled with instruments sensitive to larger particles such as optical particle sizers or aerodynamic particle sizers. Aerosol surface-area estimates have been made in this way (Maynard and Zimmer, 2002), but the necessary instrumentation array and the data inversion/interpretation are not typically well suited to routine exposure monitoring.

An intriguing approach to estimating aerosol surface-area on line has been proposed by Woo et al. (2001). If an aerosol is assumed to have a unimodal lognormal distribution, the distribution, and hence an estimation of surface-area, can be derived from just three independent measurements. Woo et al. used measurements of number concentration, mass concentration and aerosol charge to estimate surface-area. Estimates made using their method correlated well with estimates derived from size distribution measurements. Recognizing that in many occupational settings aerosol number and mass concentration may be routinely measured, but not aerosol charge, Maynard (2003) has estimated the anticipated

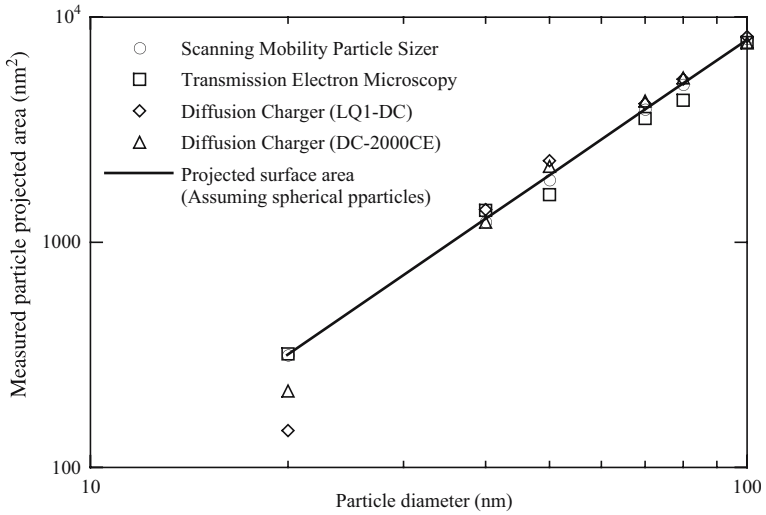

Figure 8. Comparison between methods for measuring aerosol surface-area as a function of diameter, using monodisperse particles (Ku and Maynard, 2005).

errors that would arise from using just two measurements, and assuming a width for the lognormal size distribution. In the worst case of a bimodal aerosol, it was predicted that estimates could be inaccurate by up to a factor of 10. However, simulations showed that in many cases, aerosol surface-area estimates from number and mass concentration measurements are likely to be within a factor of four of the actual surface-area. Although these errors are potentially large, they may be sufficiently small compared to the range of surface-area concentrations experienced to broadly categorize exposures.

Active (also known as *Fuchs*) surface-area represents the surface of a particle associated with molecular interactions, and may be a viable indicator of biologically relevant aerosol surface-area. For particles with Knudsen numbers (Kn, defined as the gas mean free path divided by particle radius) greater than 1, active surface-area varies as the square of particle diameter, and thus is probably a good indicator of external surface-area for nanostructured particles (Baltensperger et al., 1988). However in the continuum regime active surface area is proportional to particle diameter, and so the relationship with external particle surface-area is lost (Fuchs, 1964). The epiphaniometer (Baltensperger et al., 1988; Gäggeler et al., 1989) provides a measure of active surface-area by measuring the attachment rate of radioactive ions. Shi et al. (2001) have shown aerosol surface-area measurements made at a roadside to agree well with surface-area estimates derived from size distribution measurements. However, the epiphaniometer is not well suited to widespread use in the workplace due to its dependence on a radioactive source.

Diffusion charger-based aerosol surface-area monitors measure attachment rate using positive unipolar ions to particles (Keller et al., 2001), and thus are more amenable to use in occupational settings. Evaluation of the LQ1-DC diffusion charger (Matter Engineering, Switzerland) and DC-2000CE diffusion charger (EcoChem, USA) with spherical and fractal-like silver particles has shown a clear correlation between response and the square of particle mobility diameter for particles smaller than 100 nm (Ku and Maynard, 2005). Ku and Maynard have also shown good agreement between diffusion charger response, TEM-derived surface-area and size-distribution-derived surface-area for sub-100 nm particles (Figure 8). Above mobility diameters 100 nm, the diffusion chargers increasingly underestimate the aerosol surface-area. Measured response to monodisperse 200 nm mobility diameter particles underestimated surface-area by 40% (Ku and Maynard, 2005).

The relationship between mobility diameter and particle surface-area (Rogak et al., 1993; Ku and Maynard, 2005) indicates that aerosol mobility analysis provides an alternative approach to estimating surface-area. In theory there is a direct relationship between electrode voltage and projected surface-area in a concentric cylinder electrode differential mobility analyzer (DMA) (Ku and Maynard, 2005). Ku and Maynard have shown that deriving aerosol surface from DMA voltage can lead to substantial underestimation of surface-area when multiple charging occurs. However, for singly charged particles, this may be a viable approach to estimating aerosol surface-area. Recent developments in alternative mobility-based particle sizers such as the Opposed Migration Aerosol Classifier (Flagan, 2004) may also offer new opportunities for viable aerosol surface-area estimation.

Whichever methods of aerosol surface area measurement and characterization are developed and used, it will be essential to understand the relationship between measured parameters and biologically relevant surface area.

Exposure control

When addressing a potentially harmful exposure within a workplace, a hierarchical approach is used to reduce risk. This includes, in order of preference, the prevention or containment of hazardous workplace emissions at their source, the removal of emissions from the pathway between the source and the worker, and lastly, control of worker exposure with barriers between the worker and the hazardous work environment. This approach is consistent with that recommended by the U.S. National Institute for Occupational Safety and Health (NIOSH), which recommends the use of engineering controls over the use of personal protective equipment such as respirators to prevent worker exposure to hazardous substances (NIOSH, 1990). Engineering controls may

include: substitution for a less hazardous substance, containment of the process, isolation of the worker, ventilation to remove the hazardous substance, and associated administrative and work practice controls necessary to initiate and maintain the engineering controls (NIOSH, 1990). Establishing safe work practices, for example through worker training programs or administrative controls, is also an essential component of an effective occupational safety and health program.

The majority of aerosol control approaches and systems have been developed to address mass-based exposures, and as a result, few experimental data and evaluation protocols exist for assessing performance with respect to nanometer–diameter particles. However, aerosol theory may be used to predict the performance of control systems with some confidence. In the absence of significant thermal, electrostatic or magnetic fields, nanometer–diameter particles will closely follow the movements of air and other gases and vapors (Seinfeld and Pandis, 1998; Hinds, 1999). Thus it would seem reasonable to assume that a well designed engineering control system that is effective for gases and vapors (ACGIH, 2001) would also be effective for nanometer–diameter particles. However, further research is required on the efficacy of conventional control methods in the presence of significant phoretic fields that may occur in some workplaces. Alternatively, phoretic fields may be used as effective control mechanisms for nanometer-structured particles. For instance, electrophoresis is used in electrostatic scrubbers to remove charged particles from gases (although low charging probability at small particle sizes limits their applicability to nanometer–diameter particles) and thermophoresis can be used to prevent aerosol surface contamination in the production of semiconductors (Ye et al., 1991).

Filters are commonly used to remove aerosols particles from the air, either as part of a control system or in respirators. The properties of a filter (e.g., size of the fibers, microstructure, media thickness, electrostatic charge) determine how effective it is in removing particles (Hinds, 1999). Filter efficiency for large particles is dominated by inertial collection, and decreases with decreasing particle diameter. Nanometer diameter particles are effectively captured through diffusion, and diffusion-driven efficiency decreases with increasing particle diameter. Consequently, most air filters have a minimum collection efficiency between approximately 100 nm to 1 μm (Brown, 1993). Single fiber collection efficiency provides a good model for understanding and predicting filter performance. Lee and Liu (1982) have experimentally measured single fiber collection efficiency between 35 nm and 1.3 μm, demonstrating the

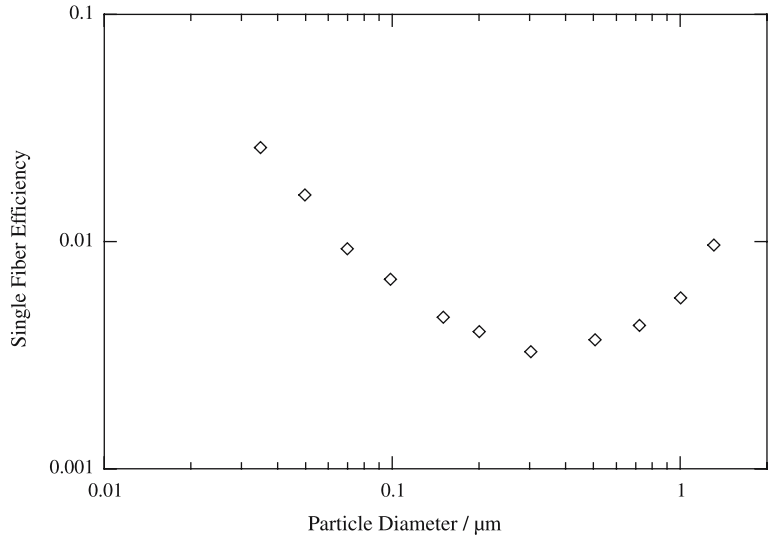

Figure 9. Experimentally measured single fiber efficiency, demonstrating a minimum collection efficiency for particles approximately 300 nm in diameter (Lee and Liu, 1982).

predicted minimum at 300 nm, and collection efficiency rising monotonically below and above this diameter (Figure 9). Although the particle diameter of minimum collection efficiency depends on a number of factors, it is typically characterized as occurring around 300 nm. Filter performance is generally evaluated using particles of this size, thus ensuring that the designated filter efficiency represents the minimum performance for particles of all sizes. For instance, high efficiency particulate air (HEPA) filters are designed to remove 99.97% of 300 nm diameter particles (DOE, 1998). Although assumptions on filter performance for nanometer–diameter particles based on diffusive capture are well founded, care should be taken when extending assumptions to filter media relying on additional mechanisms such as electrophoresis.

Some concern has been expressed that as particles approach molecular diameters, penetration may increase. The phenomenon of thermal bounce has been proposed that describes an increase in penetration as particle thermal energy overcomes the energy of attachment following initial deposition (Wang and Kasper, 1991). Studies have suggested that thermal bounce is not a concern for particles larger than a few nanometers in diameter, at least at room temperature (Wang, 1996; Pui and Chen, 2002), and VanOsdell et al. (1990) have shown good collection efficiency for liquid droplets in high efficiency filters for particles down to 4 nm in diameter. However, recent work seems to indicate that droplets smaller than approximately 20 nm penetrate pleated fibrous filters of the type used for ventilation systems (Balazy et al., 2004). Further research is required to fully understand filtration efficiency for discrete particles a few nanometers in diameter.

Working practices and mechanisms for reducing risk

If the hazard of an aerosol and the dose to workers can be assessed, then the potential risk to health can be predicted and managed more effectively. Hazard relates to the physical and chemical properties of the material (e.g., of an aerosol at the point of inhalation), and dose refers to the amount of material that enters the body or reaches a target organ (which also relates to the airborne exposure and particle physical/chemical characteristics).

Early toxicological studies of ultrafine particles in rats led Oberdörster et al. to conclude that

> "...ultrafine particles should not be considered as belonging to the category of nuisance dusts (now called PNOC, particles not otherwise classified)...", and that the "...potentially greater health hazard of ultrafine particles requires classifying them separately..." (Oberdörster et al., 1992).

While toxicological and epidemiological studies in the last decade have greatly increased our scientific understanding of the physical and chemical properties that influence the toxicity of aerosols including ultrafine particles, there remain critical data gaps regarding the nanoscale-specific hazards. Recent reviews have indicated that current knowledge is limited regarding whether existing industrial hygiene practices are adequate to assure worker health and safety in the field of nanotechnology (Aitken et al., 2004; The Royal Society and The Royal Academy of Engineering, 2004). At the same time, researchers and workers are developing, producing and using engineered nanomaterials that conceivably present an inhalation hazard, and require information on how to work with them appropriately. As a result, there is a critical need to evaluate existing studies to determine what can be learned about the potential hazard of nanomaterials and the potential risk to workers at workplace exposures, and to identify data gaps that must be filled through new research.

In response to current information needs, The UK Health and Safety Executive have published reviews of current knowledge on nanotechnology and occupational hygiene (Aitken et al., 2004) and the health effects of particles associated with nanotechnology (HSE, 2004a), along with an information document on working with engineered nanomaterials (HSE, 2004b). In the U.S., the National Institute for Occupational Safety and Health (NIOSH) have likewise begun the process of assessing the potential health hazard of nanomaterials and providing information on working safely with engineered nanomaterials (NIOSH, 2004).

These documents predominantly highlight issues of concern when working with engineered nanomaterials. Until a number of key research

gaps are filled, it is unlikely that rigorous, specific guidelines or working practices can be fully developed. However, it may be possible to identify guiding principles that will support the development of interim working practices until further quantitative information is available. Based on available information relevant to nanostructured aerosol toxicity, generation, transformation, exposure and control, it is likely that preliminary working practices will address issues such as:

- The propensity of a nanomaterial to release inhalable and respirable particles into the air during manufacturing, handling or cleanup.
- Attributes of released airborne particles such as small diameters, nanostructure, high surface-area, unique surface chemistry and other size and structure related properties that may lead to differences in hazard when compared to that for the component chemicals.
- Attributes of released aerosol particles that indicate the use of exposure metrics other than mass-based metrics.
- Whether relationships between different exposure metrics such as specific surface area will enable the extension of conventional mass-based exposure monitoring approaches to airborne engineered nanomaterials.
- Appropriate measures that can be taken to characterize and reduce or eliminate exposure.

Many of the issues currently faced when working with engineered nanomaterials parallel those associated with the development and use of new chemicals that present undefined exposure risks. One approach to working safely with such chemicals led to the development of a control evaluation approach known as control banding (Naumann et al., 1996; Oldershaw, 2001; Money, 2003). This has been developed into a framework for developing appropriate strategies in the workplace to reduce exposures to appropriate levels in the absence of quantitative exposure data by the International Labor Organization (ILO), and country-specific approaches such as Containment of Substances Hazardous to Health (COSHH) in the U.K. (Garrod and Rajan-Sithamparanadarajah, 2003). Potential risk is evaluated in terms of the hazard associated with a material, the probability of its release in a form that can be inhaled (associated with volatility for liquids, or dustiness for powders) and the quantity of material being used. These factors are then used to determine an appropriate level of control – general ventilation, engineering control, containment or process and material-specific controls. Control banding as it stands does not seem directly applicable to working with emerging nanomaterials, as it relies on hazard information being available for the material in question. However, the concept of decision-making in the absence of complete information may be extendible to situations where there are indicators of the potential hazard of a new material, but limited quantitative data.

Summary

While the production and use of engineered nanostructured particles is an essential part of the ''nanotechnology revolution'', the safe and responsible use of such particles presents many challenges. Very few studies have so far addressed the potential adverse health impact of engineered nanomaterials in the workplace. However, there is a wealth of data on environmental and occupational aerosol exposures that is applicable to developing an initial assessment of potential risk and risk reduction strategies. Although current data are insufficient to provide definitive strategies for working safely with engineered nanomaterials, they do point towards the need to approach these materials with caution. The majority of published studies indicate that the toxicity of insoluble particles of similar composition increases with decreasing particle diameter and increasing particle surface area, thus challenging current mass-based risk evaluation approaches. Particle chemistry is also clearly important and in some cases may lead to a decrease in toxicity for physically similar materials, although the underlying mechanisms of toxicity are still relatively poorly understood. The very limited published data on nanostructured aerosol release into the workplace indicates release rates of respirable particles are relatively low on a mass basis. However, without information on size, chemistry and structure-dependent particle toxicity, the significance of these

findings to occupational health cannot be quantified. Methods to control airborne nanostructured particle exposure have not been well characterized at small particle diameters, although theory and limited experimental data indicate that conventional ventilation, engineering control and filtration approaches should be applicable to particles a few nanometers in diameter and larger in many cases. The exception is likely to be where electrostatic, magnetic and thermal fields strongly influence particle motion. Thus, although the complete quantitative data needed for a full risk assessment of nanomaterials may be some way off, sufficient information is available to begin preliminary assessments of hazard or risk and to develop interim working practices until further knowledge is developed. The development of responsible nanotechnology, which integrate health and safety considerations with production and application approaches, will depend on new research to address the data gaps that still remain.

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