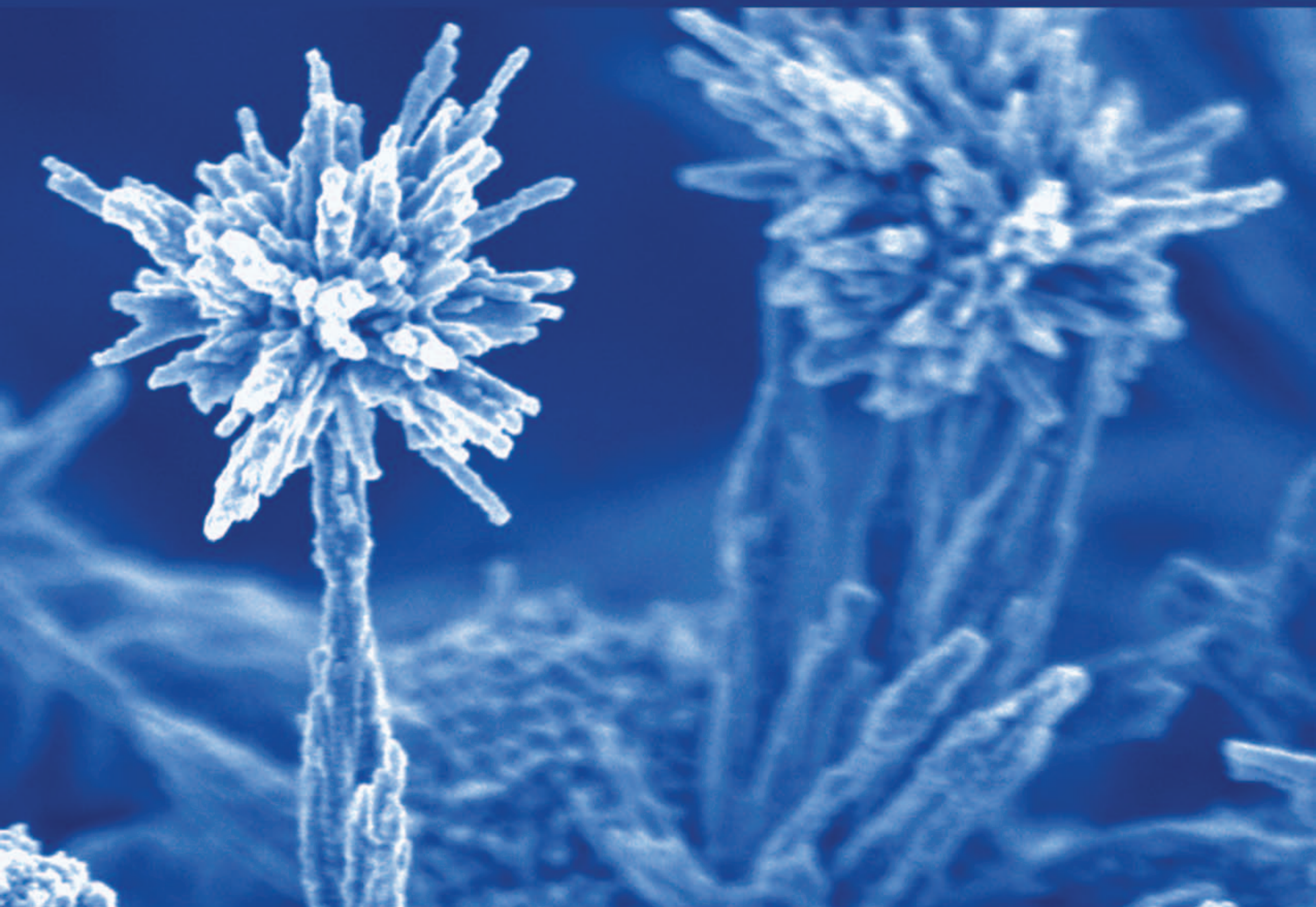
Workplace Safety and Health

Draft for Public Comment

Approaches to Safe Nanotechnology:

An Information Exchange with NIOSH



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

The *Nano Tree* shown on the cover of this document is a scanning electron microscope image of a three-dimensional nanostructure. The *trees* are nanometer scale wires of silicon carbide that are grown from droplets of Gallium metal on a silicon surface, using a gas phase fabrication method similar to that used to make current-day computer chips.

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VERSION 1.1

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We are requesting your review of this document as part of our pre-dissemination peer review. Please provide all comments, suggestions, and case studies directly to NIOSH at the following Web address for this document:

www.cdc.gov/niosh/topics/nanotech/safenano/

Feedback can be submitted using the dialogue box at the end of each section of the document.

Thank you for your participation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Director's Message

The field of nanotechnology is advancing rapidly and will likely revolutionize a broad range of consumer, medical, and industrial sectors. As with any new technology, we are faced with many unknowns; all of which raise questions concerning occupational safety and health. The National Institute for Occupational Safety and Health (NIOSH) is committed to ensuring worker protection as nanotechnology develops.

NIOSH developed the document *Approaches to Safe Nanotechnology* in October of 2005. Now NIOSH provides a 2006 update. This is intended to be an information exchange with NIOSH to raise potential safety and health concerns from exposure to nanomaterials. The document also addresses current and future research needs essential to understanding the potential risks that nanotechnology may have to workers.

It is imperative that the scientific community come together to advance our understanding of nanotechnology and its implications in the workplace. I invite you to participate in this process and encourage you to provide feedback, comments, or suggestions regarding the *Approaches to Safe Nanotechnology* document. I also encourage you to share any relevant information or experience pertaining to the field of nanotechnology.

As our knowledge grows, NIOSH plans to provide valuable guidance to the safe handling of nanoparticles and other safe approaches to nanotechnology. This will be an effort that evolves as the technology advances and our knowledge and experience grows.

Thank you,

John Howard, M.D.
Director, National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

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VERSION 1.1

Approaches to Safe Nanotechnology: An Information Exchange with NIOSH

This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by CDC/NIOSH and should not be construed to represent any agency determination or policy.

Executive Summary

Nanotechnology has the potential to dramatically improve the effectiveness of a number of existing consumer and industrial products and could have a substantial impact on the development of new applications ranging from disease diagnosis and treatment to environmental remediation. Because of the broad range of possible nanotechnology applications, continued evaluation of the potential health risks associated with exposure to nanomaterials is essential to ensure their safe handling. Nanomaterials are engineered materials having at least one dimension between 1 and 100 nanometers. Nanomaterials often exhibit unique physical and chemical properties that impart specific characteristics essential in making engineered materials, but little is known about what effect these properties may have on human health. Research has shown that the physiochemical characteristics of particles can influence their effects in biological systems. These characteristics include: particle size, shape, surface area, charge, chemical properties, solubility, and degree of agglomeration. Until the results from research studies can fully elucidate the characteristics of nanoparticles that may potentially pose a health risk, precautionary measures are warranted.

NIOSH has developed this document to provide an overview of what is known about nanomaterial hazard and measures that can be taken to minimize workplace exposures. NIOSH is seeking comments from occupational safety and health practitioners, researchers, product innovators and manufacturers, employers, workers, interest group members, and the general public so that appropriate existing health and safety guidance can be further refined and disseminated. Opportunities to provide feedback and information are available throughout the document.

The following is a summary of findings and key recommendations:

Potential Health Concerns

- The potential for nanomaterials to enter the body is among several factors that scientists examine in determining whether such materials may pose an occupational health hazard. Nanomaterials have the greatest potential to enter the body if they are in the form of nanoparticles, agglomerates of nanoparticles, and particles from nanostructured materials that become airborne or come into contact with the skin.

- Based on results from human and animal studies, airborne nanomaterials can be inhaled and deposit in the respiratory tract; and based on animal studies, nanoparticles can enter the blood stream, and translocate to other organs.

- Experimental studies in rats have shown that equivalent mass doses of insoluble ultrafine particles (smaller than 100 nm) are more potent than large particles of similar composition in causing pulmonary inflammation and lung tumors in those laboratory animals. However, toxicity may be mitigated by surface characteristics and other factors. Results from in vitro cell culture studies with similar materials are generally supportive of the biological responses observed in animals.

- Cytotoxicity and experimental animal studies have shown that changes in the chemical composition, structure of the molecules, or surfaces properties of certain nanomaterials can influence their potential toxicity.

- Studies in workers exposed to aerosols of manufactured microscopic (fine) and nanoscale (ultrafine) particles have reported lung function decrements and adverse respiratory symptoms; however, uncertainty exists about the role of ultrafine particles relative to other airborne contaminants (e.g., chemicals, fine particles) in these work environments in causing adverse health effects.

- Engineered nanoparticles whose physical and chemical characteristics are like those of ultrafine particles need to be studied to determine if they pose health risks similar to those that have been associated with the ultrafine particles.

Potential Safety Concerns

- Although insufficient information exists to predict the fire and explosion risk associated with nanoscale powders, nanoscale combustible material could present a higher risk than coarser material with a similar mass concentration given its increased particle surface area and potentially unique properties due to the nanoscale.

- Some nanomaterials may initiate catalytic reactions depending on their composition and structure that would not otherwise be anticipated from their chemical composition alone.

Working with Engineered Nanomaterials

- Nanomaterial-enabled products such as nanocomposites and surface coatings, and materials comprised of nanostructures such as integrated circuits are unlikely to pose a risk of exposure during their handling and use. However, some of the processes (formulating and applying nanoscale coatings) used in their production may lead to exposure to nanoparticles.

- Processes generating nanomaterials in the gas phase, or using or producing nanomaterials as powders or slurries/suspensions/solutions pose the greatest risk for releasing nanoparticles. Maintenance on production systems (including cleaning and disposal of materials from dust collection systems) is likely to result in exposure to nanoparticles if it involves disturbing deposited nanomaterial.
- The following workplace tasks may increase the risk of exposure to nanoparticles:
  - working with nanomaterials in liquid media without adequate protection (e.g., gloves) will increase the risk of skin exposure.
  - working with nanomaterials in liquid during pouring or mixing operations, or where a high degree of agitation is involved, will lead to an increase likelihood of inhalable and respirable droplets being formed.
  - generating nanoparticles in the gas phase in non-enclosed systems will increase the chances of aerosol release to the workplace.
  - handling nanostructured powders will lead to the possibility of aerosolization.
  - maintenance on equipment and processes used to produce or fabricate nanomaterials or the cleanup of spills or waste material will pose a potential for exposure to workers performing these tasks.
  - cleaning of dust collection systems used to capture nanoparticles can pose a potential for both skin and inhalation exposure.
  - machining, sanding, drilling, or other mechanical disruptions of materials containing nanoparticles can potentially lead to aerosolization of nanomaterials.

Exposure Assessment and Characterization

- Until more information becomes available on the mechanisms underlying nanoparticle toxicity, it is uncertain as to what measurement technique should be used to monitor exposures in the workplace. Current research indicates that mass and bulk chemistry may be less important than particle size and shape, surface area, and surface chemistry (or activity) for nanostructured materials.
- Many of the sampling techniques that are available for measuring airborne nanoaerosols vary in complexity but can provide useful information for evaluating occupational exposures with respect to particle size, mass, surface area, number concentration, composition, and surface. Unfortunately, relatively few of these techniques are readily applicable to routine exposure monitoring.
- Regardless of the metric or measurement method used for evaluating nanoaerosol exposures, it is critical that background nanoaerosol measurements be conducted before the production, processing or handling of the nanomaterial/nanoparticle.
- When feasible, personal sampling is preferred to ensure an accurate representation of the worker's exposure, whereas area sampling (e.g., size-fractionated aerosol samples) and real-time (direct

reading) exposure measurements may be more useful for evaluating the need for improvement of engineering controls and work practices.

Precautionary Measures

- Given the limited amount of information about the health risks, it is prudent to take measures to minimize worker exposures.

- For most processes and job tasks, the control of airborne exposure to nanoaerosols can be accomplished using a wide variety of engineering control techniques similar to those used in reducing exposure to general aerosols.

- The implementation of a risk management program in workplaces where exposure to nanomaterials exists can help to minimize the potential for exposure to nanoaerosols. Elements of such a program should include:

  — evaluating the hazard posed by the nanomaterial based on available physical and chemical property data and toxicology or health effects data.

  — assessing potential worker exposure to determine the degree of risk.

  — the education and training of workers in the proper handling of nanomaterials (e.g., good work practices).

  — the establishment of criteria and procedures for installing and evaluating engineering controls (e.g., exhaust, ventilation) at locations where exposure to nanoparticles might occur.

  — the development of procedures for determining the need and selection of personal protective equipment (e.g., clothing, gloves, respirators).

  — the systematic evaluation of exposures to ensure that control measures are working properly and that workers are being provided the appropriate personal protective equipment.

- Engineering control techniques such as source enclosure (i.e., isolating the generation source from the worker) and local exhaust ventilation systems should be effective for capturing airborne nanoparticles. Current knowledge indicates that a well-designed exhaust ventilation system with a high-efficiency particulate air (HEPA) filter should effectively remove nanoparticles.

- The use of good work practices can help to minimize worker exposures to nanomaterials. Examples of good practices include; cleaning of work areas using HEPA vacuum pickup and wet wiping methods, preventing the consumption of food or beverages in workplaces where nanomaterials are handled, and providing hand-washing facilities and facilities for showering and changing clothes.

- No guidelines are currently available on the selection of clothing or other apparel (e.g. gloves) for the prevention of dermal exposure to nanoaerosols. However, some clothing standards incorporate testing with nanoscale particles and therefore provide some indication of the effectiveness of protective clothing with regard to nanoparticles.

- Respirators may be necessary when engineering and administrative controls do not adequately prevent exposures. Currently, there are no specific exposure limits for airborne exposures to engineered nanoparticles although occupational exposure limits exist for larger particles of similar chemical composition. The decision to use respiratory protection should be based on professional judgment that takes into account toxicity information, exposure measurement data, and the frequency and likelihood of the worker's exposure. Preliminary evidence shows that for respirator filtration media there is no deviation from the classical single-fiber theory for particulates as small as 2.5 nm in diameter. While this evidence needs confirmation, it is likely that NIOSH certified respirators will be useful for protecting workers from nanoparticle inhalation when properly selected and fit tested as part of a complete respiratory protection program.

Occupational Health Surveillance

The unique physical and chemical properties of nanomaterials, the increasing growth of nanotechnology in the workplace, available information about biological and health effects in animals associated with exposures to some types of engineered nanoparticles in laboratory studies, and available information about the occupational health effects of incidental ultrafine particles all underscore the need for medical and hazard surveillance for nanotechnology. Every workplace dealing with nanoparticles, engineered nanomaterials, or other aspects of nanotechnology should consider the need for an occupational health surveillance program. NIOSH is in the process of formulating guidance relevant to occupational health surveillance for nanotechnology.

Introduction

Nanotechnology is the manipulation of matter on a near-atomic scale to produce new structures, materials, and devices. This technology has the ability to transform many industries and to be applied in many ways to areas ranging from medicine to manufacturing. Research in nanoscale technologies is growing rapidly worldwide. By 2015, the National Science Foundation estimates that nanotechnology will have a $1 trillion impact on the global economy and will employ 2 million workers, 1 million of which may be in the United States [Roco and Bainbridge 2001].

Nanomaterials present new challenges to understanding, predicting, and managing potential health risks to workers. As with any new material being developed, scientific data on the health effects in exposed workers are largely unavailable. **In the case of nanomaterials, the uncertainties are great because the characteristics of nanomaterials may be different from those of the larger materials with the same chemical composition.** Safety and health practitioners recognize the critical lack of guidance on the safe handling of nanomaterials—especially now, when the degree of risk to exposed workers is unknown. In the meantime, the extensive scientific literature on airborne particles—including toxicology and epidemiological studies, measurement techniques, and engineering controls—provides the best available data from which to develop interim approaches for working safely with nanomaterials and to develop hypotheses for studies of new nanomaterials.

The National Institute for Occupational Safety and Health (NIOSH) is working in parallel with the development and implementation of commercial nanotechnology through (1) conducting strategic planning and research, (2) partnering with public- and private-sector colleagues from the United States and abroad, and (3) making information widely available. The NIOSH goal is to provide national and world leadership for incorporating research findings about the implications and applications of nanotechnology into good occupational safety and health practice for the benefit of all nanotechnology workers.

Intent and Purpose

With the launch of the *Approaches to Safe Nanotechnology* Web page, NIOSH hopes to do the following:

- **Raise awareness** of the occupational safety and health issues being identified in the rapidly moving and changing science involving implications and applications of nanotechnology.
- **Use the best information available to make interim recommendations** on occupational safety and health practices in the production and use of nanomaterials. These interim recommendations will be updated as appropriate to reflect new information. They will address key components of occupational safety and health, including monitoring, engineering controls, personal protective equipment, occupational exposure limits, and administrative controls. They will draw from the ongoing NIOSH assessment of current best practices, technical knowledge, and professional judgment. Throughout the development of these guidelines, the utility of a hazard-based approach to risk assessment and control will be evaluated and, where appropriate, recommended.
- **Facilitate an exchange of information** between NIOSH and its external partners from ongoing research, including success stories, applications, and case studies.

- **Respond to requests** from industry, labor, academia, and other partners who are seeking science-based, authoritative guidelines.
- **Identify information gaps** where few or no data exist and where research is needed.

The NIOSH Web site (www.cdc.gov/niosh/topics/nanotech/) will serve as a starting point for developing good work practices and will set a foundation for developing proactive strategies for the responsible development of nanotechnologies in the U.S. workplace. This site will be dynamic in soliciting stakeholder input and featuring regular updates.

Scope

This document has been developed to provide a resource for stakeholders who wish to understand more about the safety and health applications and implications of nanotechnology in the workplace. The information and guidelines presented here are intended to aid in evaluating the potential hazard of exposure to engineered nanomaterials and to set the stage for the development of more comprehensive guidelines for reducing potential workplace exposures in the wide range of tasks and processes that use nanomaterials. The information in this document will be of specific interest to the following:

- Occupational safety and health professionals who must (1) understand how nanotechnology may affect occupational health and (2) devise strategies for working safely with nanomaterials
- Researchers working with or planning to work with engineered nanomaterials and studying the potential occupational safety and health impacts of nanomaterials
- Policy and decision-makers in government agencies and industry
- Risk evaluation professionals
- People working with or potentially exposed to engineered nanomaterials in the workplace

In making this document available, NIOSH is requesting data and information from key stakeholders that is relevant to the development of occupational safety and health guidelines. The purpose will be to develop a complete resource of occupational safety and health information and recommendations for working safely with nanomaterials based on the best available science. Particular attention will be given to questions about the potential health risks associated with exposure to nanoparticles and to the steps that can be taken to protect worker health. The information provided in this document has been abstracted from peer-reviewed literature currently available. **This document and resulting guidelines will be systematically updated by NIOSH as new information becomes available from NIOSH research or others in the scientific community.**

Established safe work practices are generally based on an understanding of the hazards associated with the chemical and physical properties of a material. Engineered nanomaterials may exhibit unique properties that are related to their physical size, shape, and structure as well as chemical composition. Considerable uncertainty still exists as to whether these unique properties involve occupational health risks. Current information about the potential adverse health effects of engineered nanomaterials, exposure assessment, and exposure control is limited. However, the large body of scientific literature that exists on exposures and responses to ultrafine and other airborne particles in animals and humans may be useful in making preliminary assessments as to the health risks posed by engineered nanomaterials. **Until further information is available, interim safe working practices should be**

developed based on the best available information. The information and recommendations in this document are intended to aid in assessment of the potential hazard of engineered nanomaterials and to set the stage for the development of more comprehensive guidelines for reducing potential workplace exposures.

Descriptions and Definitions

Nanotechnology involves the manipulation of matter at nanometer* scales to produce new materials, structures, and devices. The U.S. National Nanotechnology Initiative (NNI) (see nano.gov/html/facts/whatIsNano.html) defines a technology as nanotechnology only if it involves all of the following:

1. Research and technology development involving structures with at least one dimension in the range of 1 to 100 nanometers (nm), frequently with atomic/molecular precision
2. Creating and using structures, devices, and systems that have unique properties and functions because of their nanometer-scale dimensions
3. The ability to control or manipulate on the atomic scale

Nanotechnology is an enabling technology that offers the potential for unprecedented advances in many diverse fields. The ability to manipulate matter at the atomic or molecular scale makes it possible to form new materials, structures, and devices that exploit the unique physical and chemical properties associated with nanometer-scale structures. The promise of nanotechnology goes far beyond extending the use of current materials. New materials and devices with intricate and closely engineered structures will allow for (1) new directions in optics, electronics, and optoelectronics; (2) development of new medical imaging and treatment technologies; and (3) production of advanced materials with unique properties and high-efficiency energy storage and generation.

*1 nanometer (nm) = 1 billionth of a meter (10^{-9}).

Although nanotechnology-based products are generally thought to be at the pre-competitive stage, an increasing number of products and materials are becoming commercially available. These include nanoscale powders, solutions, and suspensions of nanoscale materials as well as composite materials and devices having a nanostructure. An inventory of such products was compiled by the Woodrow Wilson Center's Project on Emerging Nanotechnologies (www.nanotechproject.org/44/consumer-nanotechnology).

Nanoscale titanium dioxide, for instance, is finding uses in cosmetics, sun-block creams, and self-cleaning windows. And nanoscale silica is being used as filler in a range of products, including dental fillings. Recently, a number of new or "improved" consumer products using nanotechnology have entered the market—for example, stain and wrinkle-free fabrics incorporating "nanowhiskers," and longer-lasting tennis balls using butyl-rubber/nanoclay composites. Issues have been raised about the adequacy of testing and labeling requirements for nanomaterials used in consumer products [The Royal Society, The Royal Academy of Engineering 2004]. Further details on current and anticipated products can be found at www.nano.gov/html/facts/appsprod.html and www.nanotechproject.org/44/consumer-nanotechnology.

A. Nanoparticles

Nanoparticles are particles having a diameter between 1 and 100 nm. Nanoparticles may be suspended in a gas (as an nanoaerosol), suspended in a liquid (as a colloid or nanohydrosol),or embedded in a matrix (as a nanocomposite). The precise definition of “particle diameter” depends on particle shape as well as how the diameter is measured. Particle morphologies may vary widely at the nanoscale. For instance, carbon fullerenes represent nanoparticles with identical dimensions in all directions (i.e., spherical), whereas single-walled carbon nanotubes (SWCNTs) typically form convoluted, fiber-like nanoparticles with a diameter below 100 nm. Many regular but nonspherical particle morphologies can be engineered at the nanoscale, including “flower” and “belt”-like structures. For examples of some nanoscale structures, see www.nanoscience.gatech.edu/zlwang/research.html

B. Ultrafine Particles

The term “ultrafine particle” has traditionally been used by the aerosol research and occupational and environmental health communities to describe airborne particles typically smaller than 100 nm in diameter. Although no formal distinction exists between ultrafine particles and nanoparticles, **the term “ultrafine” is frequently used in the context of nanometer-diameter particles that have not been intentionally produced but are the incidental products of processes involving combustion, welding, or diesel engines.** Likewise, the term “nanoparticle” is frequently used with respect to particles demonstrating size-dependent physicochemical properties, particularly from a materials science perspective, although no formal definition exists. As a result, the two terms are sometimes used to differentiate between engineered (nanoparticle) and incidental (ultrafine) nanoscale particles.

It is currently unclear whether the use of source-based definitions of nanoparticles and ultrafine particles is justified from a safety and health perspective. This is particularly the case where data on nonengineered, nanometer-diameter particles are of direct relevance to the impact of engineered particles. An attempt has been made in this document to follow the general convention of preferentially using the term “nanoparticle” in the context of intentionally-produced or engineered nanoscale particles and the term “ultrafine” in the context of incidentally-produced particles (e.g., combustion products). However, this does not necessarily imply specific differences in the properties of these particles as related to hazard assessment, measurement, or control of exposures, and this remains an active area of research. “Nanoparticle” and “ultrafine” are not rigid definitions. For example, since the term “ultrafine” has been in existence longer, some intentionally-produced particles with primary particle sizes in the nanosize range (e.g., TiO_2) are often called “ultrafine” in the literature.

C. Engineered Nanoparticles

Engineered nanoparticles are intentionally produced, whereas incidental nanoscale or ultrafine particles are byproducts of processes such as combustion and vaporization. Engineered nanoparticles are designed with very specific properties (including shape, size, surface properties, and chemistry), and collections of the particles in an aerosol, colloid, or powder will reflect these properties. Incidental nanoscale particles are generated in a relatively uncontrolled manner and are usually physically and chemically heterogeneous compared with engineered nanoparticles.

D. Nanoaerosol

A nanoaerosol is a collection of nanoparticles suspended in a gas. The particles may be present as discrete nanoparticles, or as assemblies (aggregates or agglomerates) of nanoparticles.

These assemblies may have diameters larger than 100 nm. In the case of an aerosol consisting of micrometer-diameter particles formed as assemblies of nanoparticles, the definition of nanoaerosol is open to interpretation. It is generally accepted that if the nanostructure associated with the nanoparticles is accessible (through physical, chemical, or biological interactions), then the aerosol may be considered a nanoaerosol. However, if the nanostructure within individual micrometer-diameter particles does not directly influence particle behavior (for instance, if the nanoparticles were inaccessibly embedded in a solid matrix), the aerosol would not be described as a nanoaerosol.

E. Agglomerate

An agglomerate is a group of particles held together by relatively weak forces, including van der Waals forces, electrostatic forces and surface tension [ISO 2006].

F. Aggregate

An aggregate is a heterogeneous particle in which the various components are held together by relatively strong forces, and thus not easily broken apart [ISO 2006].

Potential Health Concerns

Nanotechnology is an emerging field. As such, there are many uncertainties as to whether the unique properties of engineered nanomaterials (which underpin their commercial potential) also pose occupational health risks. These uncertainties arise because of gaps in knowledge about the factors that are essential for predicting health risks—factors such as routes of exposure, translocation of materials once they enter the body, and interaction of the materials with the body's biological systems. The potential health risk following exposure to a substance is generally associated with the magnitude and duration of the exposure, the persistence of the material in the body, the inherent toxicity of the material, and the susceptibility or health status of the person. More data are needed on the health risks associated with exposure to engineered nanomaterials. Results of existing studies in animals or humans on exposure and response to ultrafine or other respirable particles provide a basis for preliminary estimates of the possible adverse health effects from exposures to similar engineered materials on a nano-scale. Experimental studies in rodents and cell cultures have shown that the toxicity of ultrafine or nanoparticles is greater than that of the same mass of larger particles of similar chemical composition [Oberdörster et al., 1992, 1994a,b; Lison et al., 1997; Tran et al., 1999, 2000; Brown et al., 2001; Duffin et al., 2002; Barlow et al. 2005]. In addition to particle surface area, other particle characteristics may influence the toxicity, including solubility, shape, and surface chemistry [Duffin et al. 2002; Oberdörster et al. 2005a; Maynard and Kuempel 2005; Donaldson et al. 2006]. More research is needed on the influence of particle properties on interactions with biological systems and the potential for adverse effects. International research strategies for evaluating the safety of nanomaterials are actively being developed through cooperative efforts [Thomas et al. 2006].

Existing toxicity information about a given material can also help provide a baseline for anticipating the possible adverse health effects that may occur from exposure to that same material on a nano-scale.

A. Exposure Routes

The most common route of exposure to airborne particles in the workplace is by inhalation. The deposition of discrete nanoparticles in the respiratory tract is determined by the particle's aerodynamic or thermodynamic diameter (depending on particle size). Agglomerates of nanoparticles will deposit according to the diameter of the agglomerate, not constituent nanoparticles. Research is still ongoing to determine the physical factors that contribute to the agglomeration and de-agglomeration of nanoparticles, and the role of agglomerates in the toxicity of inhaled nanoparticles.

Discrete nanoparticles are deposited in the lungs to a greater extent than larger respirable particles [ICRP 1994], and deposition increases with exercise due to increase in breathing rate and change from nasal to mouth breathing [Jaques and Kim 2000; Daigle et al. 2003] and among persons with existing lung diseases or conditions [Brown et al. 2002]. Based on animal studies, discrete nanoparticles may enter the bloodstream from the lungs and translocate to other organs [Takenaka et al. 2001; Nemmar et al. 2002; Oberdörster et al. 2002].

Discrete nanoparticles (35-37 nm count median diameter) that deposit in the nasal region may be able to enter the brain by translocation along the olfactory nerve, as was recently observed in rats [Oberdörster et al. 2004; Oberdörster et al. 2005a]. The transport of insoluble particles from 20 to 500 nm diameter to the brain via sensory nerves (including olfactory and trigeminus) was reported in earlier studies in several animal models [De Lorenzo 1970; Adams and Bray 1983; Hunter and Dey 1998]. This exposure route has not been studied in humans, and research is continuing to evaluate its relevance.

Ingestion is another route whereby nanoparticles may enter the body. Ingestion can occur from unintentional hand to mouth transfer of materials; this can occur with traditional materials, and it is scientifically reasonable to assume that it also could happen during handling of materials that contain nanoparticles. Ingestion may also accompany inhalation exposure because particles that are cleared from the respiratory tract via the mucociliary escalator may be swallowed [ICRP 1994]. Little is known about possible adverse effects from the ingestion of nanoparticles.

Some studies suggest that nanoparticles also could enter the body through the skin during occupational exposure. The U.K. Royal Society and Royal Academy of Engineers have reported that unpublished studies indicate nanoparticles of titanium dioxide used in sunscreens do not penetrate beyond the epidermis [The Royal Society and The Royal Academy of Engineering 2004]. However, the report also makes a number of recommendations addressing the need for further and more transparent information in the area of nanoparticle dermal penetration. Tinkle et al. [2003] have shown that particles smaller than 1 μm in diameter may penetrate into mechanically flexed skin samples.

A more recent study reported that nanoparticles with varying physicochemical properties were able to penetrate the intact skin of pigs (Ryman-Rasmussen et al. 2006). These nanoparticles were quantum dots of different size, shape, and surface coatings. They were reported to penetrate the stratum corenum barrier by passive diffusion and localize within the epidermal and dermal layers within 8 to 24 hours. The dosing solutions were two- to four-fold dilutions of quantum dots as commercially supplied and thus represent occupationally relevant doses. This study suggests that the skin is a potential route of exposure for nanoparticles.

At this time, it is not known if skin penetration of nanoparticles would result in adverse effects as these studies have not been reported in animal models. Studies conducted *in vitro* using primary or cultured human skin cells have shown that both SWCNT and multi-walled carbon nanotubes (MWCNT) can enter cells and cause release of pro-inflammatory cytokines, oxidative stress, and decreased viability [Monteiro-Riviere et al. 2005; Shvedova et al. 2003]. It remains unclear, however, how these findings may be extrapolated to a potential occupational risk, given that additional data are not yet available for comparing the cell model studies with actual conditions of occupational exposure. Research on the dermal exposure of nanoparticles is ongoing [www.uni-leipzig.de/~nanoderm/].

B. Effects Seen in Animal Studies

Experimental studies in rats have shown that at equivalent mass doses, insoluble ultrafine particles are more potent than larger particles of similar composition in causing pulmonary inflammation, tissue damage, and lung tumors [Lee et al. 1985; Oberdörster and Yu 1990; Oberdörster et al. 1992, 1994a,b; Heinrich et al. 1995; Driscoll 1996; Lison et al. 1997; Tran et al. 1999, 2000; Brown et al. 2001; Duffin et al. 2002; Renwick et al. 2004; Barlow et al. 2005]. These studies have shown that for poorly-soluble and low toxicity (PSLT) particles, the dose-response relationships are consistent across particle sizes when dose is expressed as particle surface area. In addition to particle size and surface area, studies have also shown that other particle characteristics can influence toxicity. For example, although the relationship between particle surface area dose and pulmonary inflammation is consistent among PSLT particles, crystalline silica is much more inflammogenic than PSLT particles at a given surface area dose [Duffin et al. 2002].

These studies indicate that for nanoparticles with similar properties (e.g., PSLT), the toxicity of a given mass dose will increase with decreasing particle size due to the increasing surface area. However, the dose-response relationship may differ for particles with different chemical composition and other properties. Consistent with these findings, a recent study reported doses of either fine or ultrafine TiO_2 in rats at which the lung responses did not significantly differ from controls, while crystalline silica caused more severe lung responses at the same dose [Warheit et al. 2006]. That study was unable to adequately test hypotheses about particle surface area dose and toxicity because the rat lung responses to either fine or ultrafine TiO_2 did not significantly differ from controls.

PTFE fume

Among ultrafine particles, freshly-generated polytetrafluoroethylene (PTFE) fume (generated at temperatures >425°C) is known to be highly toxic to the lungs. Freshly-generated PTFE fume caused hemorrhagic pulmonary edema and death in rats exposed to less than 60 $\mu g/m^3$ [Oberdörster et al. 1995]. In contrast, aged PTFE fume was much less toxic and did not result in mortality, which was attributed to the increase in particle size from accumulation and to changes in surface chemistry [Johnston et al. 2000; Oberdörster et al. 2005a]. Human case studies have reported pulmonary edema in workers exposed to PTFE fume and an accidental death in a worker when an equipment malfunction caused overheating of the PTFE resin and release of the PTFE pyrolysis products in the workplace [Goldstein et al. 1987; Lee et al. 1997]. While PTFE fume differs from engineered nanoparticles, these studies illustrate properties of ultrafine particles that have been associated with an acute toxic hazard. Enclosed processes and other engineering controls appear to have been effective at eliminating worker exposures to PTFE fume in normal operations, and thus may provide examples of control systems that may be implemented to prevent exposure to nanoparticles that may have similar properties.

Carbon nanotubes

Carbon nanotubes (CNT) are specialized forms or structures of engineered nanoparticles that have had increasing production and use [Donaldson et al. 2006]. Consequently, a number of toxicological studies of CNT have been performed in recent years. These studies have shown that the toxicity of CNT may differ from that of other nanoparticles of similar chemical composition. For example, single-walled CNTs (SWCNT) have been shown to produce adverse effects including granulomas in the lungs of mice and rats at mass doses at which ultrafine carbon black did not produce these adverse effects [Shvedova et al. 2005; Lam et al. 2004]. While both SWCNTs and carbon black are carbon-based, SWCNTs have a unique convoluted fibrous structure and specific surface chemistry that offers excellent electrical conductive properties. How these characteristics may influence toxicity is not known. CNTs may contain metal catalysts as byproducts of their production, which could also contribute to their toxicity.

In a study of SWCNTs instilled into the lungs of rats, multi-focal granulomas (without transient inflammation or persistent lesions) were observed at doses of 1 or 5 mg/kg body weight [Warheit et al. 2004]. In a study of mice instilled with one of several types of SWCNTs (raw, purified, iron-containing, and nickel-containing) at doses of 0.1 or 0.5 mg/mouse (approximately 3 or 16 mg/kg body weight), dose-dependent epithelioid granulomas were observed at 7 days, which persisted at 90 days [Lam et al. 2004,2006]. Both the raw and purified forms produced interstitial inflammation, while mortality (5/9 mice) was observed in the high dose group of the Ni-containing SWCNT.

NIOSH researchers recently reported adverse lung effects following pharyngeal aspiration of SWCNTs in mice using doses between 10–40 μg/mouse (approximately 0.5–2 mg/kg body weight) [Shvedova et al. 2005]. The findings showed that exposure to SWCNTs in mice lead to transient pulmonary inflammation, oxidative stress, decrease in pulmonary function, decrease in bacterial clearance, and early onset of interstitial fibrosis. Deposition of agglomerates resulted in development of granulomas, while deposition of more dispersed nanotube structures resulted in the rapid development of interstitial fibrosis (within 7 days), which progressed over a 60 day post-exposure period.

SWCNT were more fibrogenic than an equal mass of either ultrafine carbon black or fine quartz [Shvedova et al. 2005; Lam et al. 2004]. Based on their findings in mice, Shvedova et al. [2005] estimated that workers may be at risk of developing lung lesions if they were exposed to SWCNT over a period of 20 days at the current OSHA Permissible Exposure Limit (PEL) for graphite (5 mg/m^3). Lam et al. [2004, 2006] provided similar estimates and suggested that the graphite PEL should not be used (e.g., on MSDS) as a safe concentration for workers exposed to CNTs. Compared to instillation, the pharyngeal aspiration technique may approximate more closely the particle deposition that occurs during inhalation, although inhalation studies of CNTs may provide more definitive information about their potential toxicity in humans [Donaldson et al. 2006].

Multi-walled CNTs (MWCNT) were recently studied by intratracheal instillation in Sprague-Dawley rats receiving either 0.5, 2, or 5 mg (approximately 2, 9, or 22 mg/kg body weight) of either ground MWCNT or unground MWCNT [Muller et al. 2005]. Both forms produced pulmonary inflammation and fibrosis. The dispersion in the lungs was greater for the ground MWCNT, and fibrotic lesions were observed in the deep lungs (alveolar region) of the ground MWCNT-treated rats, while fibrosis was primarily seen in the airways of the rats treated with unground MWCNT. The biopersistence of the unground CNT was greater than that of the ground MWCNT, with 81% vs. 36%, respectively, remaining in the lungs at day 60. At an equal mass dose, ground MWCNT produced a similar inflammatory and fibrogenic response as chrysotile asbestos and a greater response than ultrafine carbon black [Muller et al. 2005]. Effects from the vehicle (1% Tween 80) used for administering ground and ungrounded MWCNT to rats were not reported; the control group used in the study was exposed to only saline. Ground CNTs are used in polymer composites and other matrixes, and thus there is a potential for worker exposure to either ground or unground CNT.

These studies indicate the need for more data on potential exposures of workers to CNTs. Maynard et al. [2004] reported relatively low airborne mass concentrations of raw SWCNT material in one facility, although concentrations increased considerably when the material was agitated. Given the unusual toxicity of SWCNT observed in rodent lungs at relatively low mass doses and the uncertainty about potential adverse effects in workers if exposed, it is prudent to minimize worker exposure to airborne CNTs through the use of effective engineering controls, work practices, and personal protective equipment (see Section on Exposure Control Procedures).

C. Observations from Epidemiological Studies Involving Fine and Ultrafine Particles

Epidemiological studies in workers exposed to aerosols including fine and ultrafine particles have reported lung function decrements, adverse respiratory symptoms, chronic obstructive pulmonary disease, and fibrosis [Kreiss et al. 1997; Gardiner et al. 2001; Antonini 2003]. In addition, some studies have found elevated lung cancer among workers exposed to certain ultrafine particles, e.g., diesel exhaust particulate [Steenland et al. 1998; Garshick et al. 2004] or welding fumes [Antonini 2003]. The implications of these studies to engineered nanoparticles, which may have different particle properties, are uncertain.

Epidemiological studies in the general population have shown associations between particulate air pollution and increased morbidity and mortality from respiratory and cardiovascular diseases [Dockery et al. 1993; HEI 2000; Pope et al. 2002; Pope et al. 2004]. Some epidemiological studies have shown adverse health effects associated with exposure to the ultrafine particulate fraction of air pollution [Peters et al. 1997; Penttinen et al. 2001; Ibald-Mulli et al. 2002; Timonen et al. 2004; Ruckerl et al. 2005], although uncertainty exists about the role of ultrafine particles relative to the other air pollutants in causing the observed adverse health effects. The associations in these studies have been based on measurements of the particle number or mass concentrations of particles within certain size fractions (e.g., PM2.5). In an experimental study of healthy and asthmatic subjects inhaling ultrafine carbon particles, changes were observed in the expression of adhesion molecules by blood leukocyte, which may relate to possible cardiovascular effects of ultrafine particle exposure [Frampton et al. 2006].

D. Hypotheses from Animal and Epidemiological Studies

The existing literature on particles and fibers provides a scientific basis from which to evaluate the potential hazards of engineered nanoparticles. While the properties of engineered nanoparticles can vary widely, the basic physicochemical and toxicokinetic principles learned from the existing studies are relevant to understanding the potential toxicity of nanoparticles. For example, we know from studies in humans that a greater proportion of inhaled nanoparticles will deposit in the respiratory tract (both at rest and with exercise) compared to larger particles [ICRP 1994; Jaques and Kim 2000; Daigle et al. 2003; Kim and Jaques 2004]. We know from studies in animals that nanoparticles in the lungs can be translocated to other organs in the body, although it is not well known how this may be influenced by the chemical and physical properties of the nanoparticles [Takenaka et al. 2001; Kreyling et al. 2002; Oberdörster et al. 2002, 2004; Semmler et al. 2004; Geiser et al. 2005]. Due to their small size, nanoparticles can cross cell membranes and interact with subcellular structures such as mitochondria, where they have been shown to cause oxidative damage and impair function of cells in culture [Möller et al. 2002, 2005; Li et al. 2003; Geiser et al. 2005]. Animal studies have shown that nanoparticles are more biologically active due to their greater surface area per mass compared with larger-sized particles of the same chemistry [Oberdörster et al. 1992; 1994a,b; 2005a; Driscoll 1996; Lison et al. 1997; Brown et al. 2001; Duffin et al. 2002; Renwick et al. *2004*; Barlow et al. 2005]. While this increased biological activity of nanoparticles is a fundamental component to the utility of nanoparticles for industrial, commercial, and medical applications, the consequences of unintentional exposures of workers to nanoparticles are uncertain.

Research reported from laboratory animal studies and from human epidemiological studies have lead to hypotheses regarding the potential adverse health effects of engineered nanoparticles. These hypotheses are based on the scientific literature of particle exposures in animals and humans. This literature has been recently reviewed [Donaldson et al. 2005; Maynard and Kuempel 2005; Oberdörster et al. 2005a, Donaldson et al. 2006; Kreyling et al. 2006]. In general, the particles used in past studies have not been characterized to the extent recommended for new studies in order to more fully understand the particle properties influencing toxicity [Oberdörster et al. 2005b; Thomas et al. 2006]. As this research continues, more data will become available to support or refute these hypotheses for engineered nanoparticles.

1. **Exposure to engineered nanoparticles is likely to cause adverse health effects similar to well-characterized ultrafine particles that have similar physical and chemical characteristics.**

Studies in rodents and humans support the hypothesis that exposure to incidental ultrafine particles pose a greater respiratory hazard than the same mass of larger particles with a similar chemical composition. Studies of existing particles have shown adverse health effects in workers exposed to ultrafine particles (e.g., diesel exhaust particulate, welding fumes), and animal studies have shown that ultrafine particles are more inflammogenic and tumorigenic in the lungs of rats than an equal mass of larger particles of similar composition [Oberdörster and Yu 1990; Driscoll 1996; Tran et al. 1999, 2000]. **If engineered nanoparticles have the same physiochemical characteristics that are associated with reported effects from ultrafine particles, they may also pose the same health concerns.**

Although the physiochemical characteristics of existing ultrafine particles and engineered nanoparticles can differ substantially, the toxicological and dosimetric principles derived from available studies may be relevant to postulating the health concerns for new engineered particles. The biological mechanisms of particle-related lung diseases (e.g., oxidative stress, inflammation, and production of cytokines, chemokines, and cell growth factors) [Mossman and Churg 1998; Castranova 2000, Donaldson and Tran 2002] appear to be a consistent lung response for respirable particles including ultrafine or nanoparticles [Donaldson et al. 1998; Donaldson and Stone 2003; Oberdörster et al. 2005]. Toxicological studies have shown that the chemical and physical properties that are important factors influencing the fate and toxicity of ultrafine particles may also be significant for other nanoparticles [Duffin et al. 2002; Kreyling et al. 2002; Oberdörster et al. 2002; Semmler et al. 2004].

2. **Surface area and activity, particle number may be better predictors of potential hazard than mass.**

The greater potential hazard may relate to the greater number or surface area of nanoparticles compared with that for the same mass concentration of larger particles [Oberdörster et al. 1992; Oberdörster et al. 1994a,b; Driscoll et al. 1996; Tran et al. 2000; Brown et al. 2001; Peters et al. 1997; Moshammer and Neuberger 2003]. This hypothesis is based primarily on the pulmonary effects observed in studies of rodents exposed to various types of ultrafine or fine particles (e.g., titanium dioxide, carbon black, barium sulfate, diesel soot, coal fly ash, and toner) and in humans exposed to aerosols including nanoparticles (e.g., diesel exhaust and welding fumes). These studies indicate that for a given mass of particles, relatively insoluble nanoparticles are more toxic than larger particles of similar chemical composition and surface properties. Studies of fine and ultrafine particles have shown that particles with less biologically reactive surfaces are less toxic [Tran et al. 1999; Duffin et al. 2002]. However, even particles with low inherent toxicity (e.g., titanium dioxide) have been shown to cause pulmonary inflammation, tissue damage, and fibrosis at sufficiently high particle surface area doses [Oberdörster et al. 1992, 1994a,b; Tran et al. 1999, 2000].

Through engineering, the properties of nanomaterials can be modified. For example, a recent study has shown that the cytotoxicity of water-soluble fullerenes can be reduced by several orders of magnitude by modifying the structure of the fullerene molecules (e.g., by hydroxylation) [Sayes et al. 2004]. These structural modifications were shown to reduce the cytotoxicity by reducing the generation of oxygen radicals—which is a probable mechanism by which cell membrane damage and death occurred in these cell cultures. Increasing the sidewall functionalization of SWCNT also rendered these nanomaterials less cytotoxic to cells in culture [Sayes et al. 2005]. Cytotoxicity studies with quantum dots have shown that the type of surface coating can have a significant effect on cell motility and viability [Hoshino et al. 2004; Shiohara et al. 2004; Lovric et al. 2005]. Differences in the phase composition of nanocrystalline structures can influence their cytotoxicity; in a recent study comparing two types of titanium dioxide nanoparticles, anatase was more cytotoxic and produced more reactive species than did rutile with similar specific surface area (153 and 123 m^2g, respectively) [Sayes et al. 2006]. Reactive oxygen species were also associated with the cytotoxicity of titanium dioxide nanoparticles to mouse microglia (brain cells) grown in culture [Long et al. 2006].

The studies of ultrafine particles may provide useful data to develop preliminary hazard or risk assessments and to generate hypotheses for further testing. The studies in cell cultures provide information about the cytotoxic properties of nanomaterials that can guide further research and toxicity testing in whole organisms. More research is needed of the specific particle properties and other factors that influence the toxicity and disease development associated with airborne particles, including those characteristics that may be most predictive of the potential safety or toxicity of new engineered nanoparticles.

Potential Safety Hazards

Very little is known about the safety risks that engineered nanomaterials might pose, beyond some data indicating that they possess certain properties associated with safety hazards in traditional materials. From currently available information, the potential safety concerns most likely would involve catalytic effects or fire and explosion hazards if nanomaterials are found to behave similarly to traditional materials in key respects.

A. Fire and Explosion

Although insufficient information exists to predict the fire and explosion risk associated with nanoscale powders, **nanoscale combustible material could present a higher risk than coarser material of similar quantity given its unique properties** [HSE 2004]. Decreasing the particle size of combustible materials can reduce minimum ignition energy and increase combustion potential and combustion rate, leading to the possibility of relatively inert materials becoming highly combustible. Dispersions of combustible nanomaterial in air may present a greater safety risk than dispersions of non-nanomaterials with similar compositions. Some nanomaterials are designed to generate heat through the progression of reactions at the nanoscale. Such materials may present a fire hazard that is unique to engineered nanomaterials. **In the case of some metals, explosion risk can increase significantly as particle size decreases.**

The greater activity of nanoscale materials forms a basis for research into nanoenergetics. For instance, nanoscale Al/MoO_3 thermites ignite more than 300 times faster than corresponding micrometer-scale material [Granier and Pantoya 2004].

B. Catalytic reaction

Nanometer-diameter particles and nanostructured porous materials have been used for many years as effective catalysts for increasing the rate of reactions or decreasing the necessary temperature for reactions to occur in liquids and gases. **Depending on their composition and structure, some nanomaterials may initiate catalytic reactions and increase their fire and explosion potential that would not otherwise be anticipated from their chemical composition alone** [Pritchard 2004].

Guidelines for Working with Engineered Nanomaterials

Engineered nanomaterials are diverse in their physical, chemical, and biological nature. The processes used in research, material development, production, and use or introduction of nanomaterials have the potential to vary greatly. **Until further information on the possible health risks and extent of occupational exposure to nanomaterials becomes available, interim precautionary measures should be developed and implemented.** These measures should focus on the development of safe working practices tailored to the specific processes and materials where workers might be exposed. Hazard information that is available about common materials that are being manufactured in the nanometer range (for example, TiO_2) should be considered as a starting point in developing appropriate work practices and controls.

The following guidelines are designed to aid in the assessment of hazard for engineered nanomaterials and for reducing exposures in the workplace. Using a hazard-based approach to evaluate exposures and for developing precautionary measures is consistent with good occupational safety and health practices, such as those recommended by the UK Royal Society and Royal Academy of Engineers [The Royal Society and The Royal Academy of Engineering 2004].

A. Potential for Occupational Exposure

Few workplace measurement data exist on airborne exposure to nanoparticles that are purposely produced and not incidental to an industrial process. In general, it is likely that processes generating nanomaterials in the gas phase, or using or producing nanomaterials as powders or slurries/suspensions/solutions (i.e. in liquid media) pose the greatest risk for releasing nanoparticles. In addition, **maintenance on production systems (including cleaning and disposal of materials from dust collection systems) is likely to result in exposure to nanoparticles if it involves disturbing deposited nanomaterial.** Exposures associated with waste streams containing nanomaterials may also occur.

The magnitude of exposure to nanoparticles when working with nanopowders depends on the likelihood of particles being released from the powders during handling. NIOSH researchers are actively conducting research to quantitatively determine how various nanomaterials are comparatively dispersed. Studies on exposure to SWCNTs have indicated that although the raw material may release visible particles into the air when handled, the particle size of the agglomerate can be a few millimeters in diameter and the release rate of inhalable and respirable particles relatively low (on a mass or number basis) compared with other nanopowders; however, providing energy to the bulk dust (vortexing) generated significant levels of respirable dust [Maynard et al. 2004]. Since data are generally lacking with regard to the generation of inhalable/respirable particles during the production and use of engineered nanomaterials, further research is required to determine exposures under various conditions. NIOSH researchers are conducting both laboratory and field-based evaluations in order to address some of these knowledge gaps.

Devices comprised of nanostructures, such as integrated circuits, pose a minimal risk of exposure to nanoparticles during handling. However, some of the processes used in their production may lead to exposure to nanoparticles (for example, exposure to commercial polishing compounds that contain nanoscale particles, or exposure to nanoscale particles that are inadvertently dispersed or created during the manufacturing and handling processes). Likewise, large-scale components formed from nanocomposites will most likely not present significant exposure potential. However, if such materials are used or handled in such a manner that can generate nanostructured particles (e.g., cutting, grinding), or undergo degradation processes that lead to the release of nanostructured material, then exposure may occur by the inhalation, ingestion, and/or dermal penetration of these particles.

B. Factors Affecting Exposure to Nanoparticles

Factors affecting exposure to engineered nanoparticles include the amount of material being used and whether the material can be easily dispersed (in the case of a powder) or form airborne sprays or droplets (in the case of suspensions). The degree of containment and duration of use will also influence exposure. In the case of airborne material, particle or droplet size will determine whether the material can enter the respiratory tract and where it is most likely to deposit. Inhaled particles smaller than 10 μm in diameter have some probability of penetrating to and being deposited in the gas exchange (alveolar) region of the lungs, but there is at least a 50% probability that particles smaller than 4 μm in diameter will reach the gas-exchange region [Lippmann 1977; ICRP 1994; ISO 1995]. Particles that are capable of being deposited in the gas exchange region of the lungs are considered respirable particles. **The mass deposition fraction of nanoparticles is greater in the human respiratory tract than that for larger respirable particles.** Up to 50% of inhaled nanoparticles may deposit in the gas-exchange region [ICRP 1994]. For inhaled nanoparticles smaller than approximately 30 nm, an increasing mass fraction of particles is also predicted to deposit in the upper airways of the human respiratory tract [ICRP 1994].

At present there is insufficient information to predict all of the situations and workplace scenarios that are likely to lead to exposure to nanomaterials. However, there are some workplace factors that can increase the potential for exposure. These include:

- Working with nanomaterials in liquid media without adequate protection (e.g., gloves) will increase the risk of skin exposure.
- Working with nanomaterials in liquid media during pouring or mixing operations, or where a high degree of agitation is involved, will lead to an increased likelihood of inhalable and respirable droplets being formed.
- Generating nanoparticles in the gas phase in nonenclosed systems will increase the chances of aerosol release to the workplace.
- Handling nanostructured powders will lead to the possibility of aerosolization.
- Maintenance on equipment and processes used to produce or fabricate nanomaterials will pose a potential exposure risk to workers performing these tasks.
- Cleaning of dust collection systems used to capture nanoparticles will pose a potential for both skin and inhalation exposure.

Exposure Assessment and Characterization

There are currently no national or international consensus standards on measurement techniques for nanoparticles in the workplace. However, information and guidance for monitoring nanoparticle exposures in workplace atmospheres has recently been developed by the International Organization for Standardization and is in press [ISO 2006]. If the qualitative assessment of a process has identified potential exposure points and leads to the decision to measure nanoparticles, several factors must be kept in mind. Current research indicates that mass and bulk chemistry may be less important than particle size, surface area, and surface chemistry (or activity) for nanostructured materials [Oberdörster et al. 1992, 1994a,b; Duffin et al. 2002]. Research is ongoing into the relative importance of these different exposure metrics, and how to best characterize exposures to nanoparticles in the workplace. In addition, the unique shape and properties of some nanomaterials may pose additional challenges. For example, the techniques used to measure fiber concentrations in the workplace (e.g., phase contrast microscopy) would not be able to detect individual carbon nanotubes (diameter <100 nm), nor bundles of carbon nanotubes with diameters less than 250 nm [Donaldson et al. 2006].

A. Monitoring Workplace Exposures

While research continues to address questions of nanoparticle toxicity, a number of exposure assessment approaches can be initiated to help determine worker exposures. These assessments can be performed using traditional industrial hygiene sampling methods that include the use of samplers placed at static locations (area sampling), samples collected in the breathing zone of the worker (personal sampling), or real-time measurements of exposure that can be personal or static. In general, personal sampling is preferred to ensure an accurate representation of the worker's exposure, whereas area samples (e.g., size-fractionated aerosol samples) and real-time (direct-reading) exposure measurements may be more useful for evaluating the need for improvement of engineering controls and work practices.

Many of the sampling techniques that are available for measuring airborne nanoaerosols vary in complexity but can provide useful information for evaluating occupational exposures with respect to particle size, mass, surface area, number concentration, composition, and surface chemistry. Unfortunately, relatively few of these techniques are readily applicable to routine exposure monitoring. These measurement techniques are described below along with their applicability for monitoring nanometer aerosols.

For each measurement technique used, it is vital that the key parameters associated with the technique and sampling methodology be recorded when measuring exposure to nanoaerosols. This should include the response range of the instrumentation, whether personal or static measurements are made, and the location of all potential aerosol sources. Comprehensive documentation will facilitate comparison of exposure measurements using different instruments and exposure metrics and will aid the re-interpretation of historic data as further information is developed on appropriate exposure metrics. **Regardless of the metric and method selected for exposure monitoring, it is critical that measurements be conducted before production or processing of a nanomaterial to obtain background exposure data.** Measurements made during production or processing can then be evaluated to determine if there has been an increase in exposure from background measurements. NIOSH is presently conducting research to evaluate various measurement techniques and will release those results on this site when they become available.

Size-fractionated aerosol sampling

Studies indicate that particle size plays an important role in determining the potential adverse effects of nanoparticles in the respiratory system, by influencing the physical, chemical, and biological nature of the material; by affecting the surface area dose of deposited particles, and by enabling deposited particles to more readily translocate to other parts of the body. Animal studies indicate that the toxicity of nanometer aerosols is more closely associated with the particle surface area and particle number than with the particle mass concentration when comparing aerosols with different particle size distributions. However, mass concentration measurements may be applicable for evaluating occupational exposure to nanometer aerosols where a good correlation between the surface area of the aerosol and mass concentration can be determined or if toxicity data based on mass dose are available for a specific nanometer aerosol associated with a known process (e.g., diesel exhaust particulate).

Aerosol samples can be collected using inhalable, thoracic, or respirable samplers, depending on the region of the respiratory system most susceptible to the inhaled particles. **Current information suggests that a large fraction of inhaled nanoparticles will deposit in the gas-exchange region of the lungs [ICRP 1994], suggesting the use of respirable samplers.** Respirable fraction samplers will also collect a nominal amount of nanometer-diameter particles that can deposit in the upper airways and ultimately be cleared or transported to other parts of the body.

Respirable fraction samplers allow mass-based exposure measurements to be made using gravimetric and/or chemical analysis [NIOSH 1994a]. However, they do not provide information on aerosol number, size, or surface area concentration, unless the relationship between different exposure metrics for the aerosol (e.g., density, particle shape) has been previously characterized. Currently, no commercially available personal samplers are designed to measure the particle number, surface area, or mass concentration of nanometer aerosols. However, several methods are available that can be used to estimate surface area, number, or mass concentration for particles smaller than 100 nm.

In the absence of specific exposure limits or guidelines for engineered nanoparticles, exposure data gathered from the use of respirable samplers [NIOSH 1994b] can be used to determine the need for engineering controls or work practices and for routine exposure monitoring of processes and job tasks. When chemical components of the sample need to be identified, chemical analysis of the filter samples can permit smaller quantities of material to be quantified, with the limits of quantification depending on the technique selected [NIOSH 1994a]. The use of conventional impactor samplers to assess nanoparticle exposure is limited, to a lower collection efficiency of 200 to 300 nm. Low-pressure cascade impactors that can measure particles to 50 nm may be used for static sampling, since their size and complexity preclude their use as personal samplers [Marple et al. 2001, Hinds 1999]. A personal cascade impactor is available with a lower aerosol cut point of 250 nm [Misra et al. 2002], allowing an approximation of nanometer particle mass concentration in the worker's breathing zone. For each method, the detection limits are of the order of a few micrograms of material on a filter or collection substrate [Vaughan et al. 1989]. Cascade impactor exposure data gathered from worksites where nanomaterials are being processed or handled can be used to make assessments as to the efficacy of exposure control measures.

Real-time aerosol sampling

The real-time (direct-reading) measurement of nanometer aerosol concentrations is limited by the sensitivity of the instrument to detect small particles. Many real-time aerosol mass monitors used in the workplace rely on light scattering from groups of particles (photometers). This methodology is generally insensitive to particles smaller than 300 nm [Hinds 1999]. Optical instruments that size individual particles and convert the measured distribution to a mass concentration are similarly limited to particles larger than 100 to 300 nm. Quantitative information gained by optical particle counters may also be limited by relatively poor counting efficiencies at smaller (< 500 nm) particle diameters. Similarly, the response of optical particle counters may be highly material dependent. The Scanning Mobility Particle Sizer (SMPS) is widely used as a research tool for characterizing nanometer aerosols, although its applicability for use in the workplace may be limited because of its size, cost, and the inclusion of a radioactive source. Additionally, the SMPS may take from 2 to 3 minutes to scan an entire size distribution; thus, it may be of limited use in workplaces with highly variable aerosol size distributions, such as close to a strong particle source. Fast (< 1 second) mobility based particle sizing instruments are now available commercially; however, because they have fewer channels they lack the finer sizing resolution of the SMPS. The Electrical Low Pressure Impactor (ELPI) is an alternative instrument that combines diffusion charging and a cascade impactor with real-time (< 1 second) aerosol charge measurements providing aerosol size distributions by aerodynamic diameter [Keskinen et al. 1992].

Surface area measurements

Relatively few techniques exist to monitor exposures with respect to aerosol surface area. Isothermal adsorption is a standard off-line technique used to measure the specific surface area of powders that can be adapted to measure the specific surface area of collected aerosol samples. For example, the surface area of particulate material (e.g., using either a bulk or an aerosol sample) can be measured in the laboratory using a gas adsorption method (e.g., Brunauer, Emmett, and Teller, BET) [Brunauer et al. 1938]. However, the BET method requires relatively large quantities of material, and measurements are influenced by particle porosity and adsorption gas characteristics.

The first instrument designed to measure aerosol surface-area was the epiphaniometer [Baltensperger et al. 1988]. This device measures the Fuchs or active surface-area of the aerosols by measuring the attachment rate of radioactive ions. For aerosols less than approximately 100 nm in size, measurement of the Fuchs surface area is probably a good indicator of external surface-area (or geometric surface area). However, for aerosols greater than approximately 1 μm the relationship with geometric particle surface-area is lost [Fuchs 1964]. Measurements of active surface-area are generally insensitive to particle porosity. The epiphaniometer is not well suited to widespread use in the workplace because of the inclusion of a radioactive source and the lack of effective temporal resolution.

This same measurement principle can be applied with the use of a portable aerosol diffusion charger. Studies have shown that these devices provide a good estimate of aerosol surface area when airborne particles are smaller than 100 nm in diameter. For larger particles, diffusion chargers underestimate aerosol surface area. However, further research is needed to evaluate the degree of underestimation. Extensive field evaluations of commercial instruments are yet to be reported. However, laboratory evaluations with monodisperse silver particles have shown that 2 commercially available diffusion chargers can provide good measurement data on aerosol surface area for particles smaller than 100 nm in diameter but underestimate the aerosol surface area for particles larger than 100 nm in diameter [Ku and Maynard 2005, 2006].

Particle number concentration measurement

Particle number concentration has been associated with adverse responses to air pollution in some human studies [Timonen et al. 2004; Ruckerl et al. 2005], while in toxicological studies, particle surface area has generally been shown to be a better predictor than either particle number, mass, or volume concentration alone [Oberdörster and Yu 1990; Tran et al. 1999; Duffin et al. 2002]. A two-variable dose metric of particle size and volume was shown to be the best predictor of lung cancer in rats from various types of particles [Borm et al. 2004; Pott and Roller 2005]. This illustrates some of the complexity of interpreting the existing data on particle dose metric and response. While adverse health effects appear to be more closely related with particle surface area the number of particles depositing in the respiratory tract or other organ systems may also play an important role.

Aerosol particle number concentration can be measured relatively easily using Condensation Particle Counters (CPCs). These are available as hand-held static instruments, and they are generally sensitive to particles greater than 10 to 20 nm in diameter. CPCs designed for the workplace do not have discrete size-selective inputs, and so they are typically sensitive to particles up to micrometers in diameter. Commercial size-selective inlets are not available to restrict CPCs to the nanoparticle size range; however, the technology exists to construct size-selective inlets based on particle mobility, or possibly inertial pre-separation. An alternative approach to estimating nanoparticle concentrations using a CPC is to use the instrument in parallel with an optical particle counter. The difference in particle count between the instruments will provide an indication of particle number concentration between the lower CPC detectable particle diameter and the lower optical particle diameter (typically 300 to 500 nm).

A critical issue when characterizing exposure using particle number concentration is selectivity. **Nanoparticles are ubiquitous in many workplaces,** from sources such as combustion, vehicle emissions, and infiltration of outside air. Particle counters are generally insensitive to particle source or composition **making it difficult to differentiate between incidental and process-related nanoparticles using number concentration alone.** In a study of aerosol exposures while bagging carbon black, Kuhlbusch et al. [2004] found that peaks in number concentration measurements were associated with emissions from fork lift trucks and gas burners in the vicinity, rather than the process under investigation. In a similar manner, during an ultrafine particle mapping exercise in an automotive facility, Peters et al. [2006] found that direct gas-fired heating systems systematically produced high particle number concentrations throughout the facility where the heating system was in operation. Although this issue is not unique to particle number concentration measurements, orders of magnitude difference can exist in aerosol number concentrations depending on concomitant sources of particle emissions.

Although using nanoparticle number concentration as an exposure measurement may not be consistent with exposure metrics being used in animal toxicity studies, **such measurements may be a useful indicator for identifying nanoparticle emissions and determining the efficacy of control measures.** Portable CPCs are capable of measuring localized aerosol concentrations, allowing the assessment of particle releases occurring at various processes and job tasks [Brouwer et al. 2004].

Surface area estimation

Information about the relationship between different measurement metrics can be used for estimating aerosol surface area. If the size distribution of an aerosol remains consistent, the relationship between number, surface area, and mass metrics will be constant. In particular, mass concentration measurements can be used for deriving surface area concentrations, assuming the constant of proportionality is known. This constant is the specific surface area (surface to mass ratio).

Size distribution measurements obtained through sample analysis by transmission electron microscopy may also be used to estimate aerosol surface area. If the measurements are weighted by particle number, information about particle geometry will be needed to estimate the surface area of particles with a given diameter. If the measurements are weighted by mass, additional information about particle density will be required.

If the airborne aerosol has a lognormal size distribution, the surface-area concentration can be derived using three independent measurements. An approach has been proposed using three simultaneous measurements of aerosol that included mass concentration, number concentration, and charge [Woo et al. 2001]. With knowledge of the response function of each instrument, minimization techniques can be used to estimate the parameters of the lognormal distribution leading to the three measurements used in estimating the aerosol surface area.

An alternative approach has been proposed whereby independent measurements of aerosol number and mass concentration are made, and the surface area is estimated by assuming the geometric standard deviation of the (assumed) lognormal distribution [Maynard 2003]. This method has the advantage of simplicity by relying on portable instruments that can be used in the workplace. Theoretical calculations have shown that estimates may be up to a factor of ten different from the actual aerosol surface-area, particularly when the aerosol has a bimodal distribution. Field measurements indicate that estimates are within a factor of three of the active surface-area, particularly at higher concentrations. In workplace environments, aerosol surface-area concentrations can be expected to span up to 5 orders of magnitude; thus, surface-area estimates may be suited for initial or preliminary appraisals of occupational exposure concentrations.

Although such estimation methods are unlikely to become a long-term alternative to more accurate methods, they may provide a viable interim approach to estimating the surface area of nanometer aerosols in the absence of precise measurement data. Additional research is needed on comparing methods used for estimating aerosol surface area with a more accurate aerosol surface area measurement method. NIOSH is conducting research in this area and will communicate results as they become available. In the interim, NIOSH welcomes additional information and input on this topic.

B. Proposed Sampling Strategy

Currently, there is not one sampling method that can be used to characterize exposure to nanosized aerosols. Therefore, any attempt to characterize workplace exposure to nanoparticles must involve a multifaceted approach incorporating many of the sampling techniques mentioned above. Brouwer et al. [2004] recommend that all relevant characteristics of nanoparticle exposure be measured, and a sampling strategy similar to theirs would provide a reasonable approach to characterizing workplace exposure.

The first step would involve identifying the source of nanoparticle emissions. A CPC provides acceptable capability for this purpose. **It is critical to determine ambient or background particle counts before measuring particle counts during the manufacture or processing of the nanoparticles** involved. If a specific nanoparticle is of interest (e.g. TiO_2), then area sampling with a filter suitable for analysis by electron microscopy should also be employed. Transmission electron microscopy (TEM) can identify specific particles and can estimate the size distribution of the particles.

Once the source of emissions is identified, aerosol surface area measurements should be conducted with a portable diffusion charger and aerosol size distributions should be determined with an SMPS or ELPI using static (area) monitoring. A small portable surface area instrument could be adapted to be worn by a worker, although depending on the nature of the work, this may be cumbersome. Further, losses of aerosol with the addition of a sampling tube would need to be calculated if this were used. The location of these instruments should be considered carefully. Ideally they should be placed close to the work areas of the workers, but other factors such as size of the instrumentation, power source, etc. will need to be considered.

Lastly, personal sampling using filters or grids suitable for analysis by electron microscopy or chemical identification should be employed, particularly if measuring exposures to specific nanoparticles is of interest. Electron microscopy can be used to identify the particles, and can provide an estimate of the size distribution of the particle of interest. The use of a personal cascade impactor or a respirable cyclone sampler with a filter, though limited, will help to remove larger particles that may be of limited interest and allow a more definitive determination of particle size. Analysis of these filters for air contaminants of interest can help identify the source of the respirable particles. Standard analytical chemical methodologies should be employed [NIOSH 1994a].

By using a combination of these techniques, an assessment of worker exposure to nanoparticles can be conducted. This approach will allow a determination of the presence and identification of nanoparticles and the characterization of the important aerosol metrics. However, since this approach relies primarily on static or area sampling some uncertainty will exist in estimating worker exposures.

Exposure Control Procedures

Given the limited information about the health risks associated with occupational exposure to engineered nanoparticles, work practices and engineering controls should be tailored to the processes and job tasks in which exposure might occur. **For most processes and job tasks, the control of airborne exposure to nanoparticles can most likely be accomplished using a wide variety of engineering control techniques similar to those used in reducing exposures to general aerosols** [Ratherman 1996; Burton 1997]. To ensure that the appropriate steps are taken to minimize the risk of exposure, a risk management program should be implemented. Elements of such a program should include the establishment of guidelines for installing and evaluating engineering controls (e.g., exhaust ventilation), the education and training of workers in the proper handling of nanomaterials (e.g., good work practices), and the development of procedures for selecting and using personal protective equipment (e.g., clothing, gloves, respirators).

A. Engineering Controls

In general, control techniques such as source enclosure (i.e., isolating the generation source from the worker) and local exhaust ventilation systems should be effective for capturing airborne nanoparticles, based on what is known of nanoparticle motion and behavior in air. The use of ventilation systems should be designed, tested, and maintained using approaches recommended by the American Conference of Governmental Industrial Hygienists [ACGIH 2001]. In light of current scientific knowledge about the generation, transport, and capture of aerosols, these control techniques should be effective for controlling airborne exposures to nanometer-scale particles [Seinfeld and Pandis 1998; Hinds 1999].

Dust collection efficiency of filters

Current knowledge indicates that a well-designed exhaust ventilation system with a high- efficiency particulate air (HEPA) filter should effectively remove nanoparticles [Hinds 1999]. Filters are tested using particles that have the lowest probability of being captured (typically around 300 nm in diameter). It is expected that the collection efficiencies for smaller particles should exceed the measured collection efficiency at this particle diameter [Lee and Liu 1982]. NIOSH is conducting research to validate the efficiency of HEPA filter media used in environmental control systems and in respirators in removing nanoparticles. As results of this research become available, they will be posted on the NIOSH Web site.

If HEPA filters are used in the dust collection system, they should be coupled to a well-designed filter housing. If the filter is improperly seated, nanoparticles have the potential to bypass the filter, leading to filter efficiencies much less than predicted [NIOSH 2003].

B. Work Practices

The incorporation of good work practices in a risk management program can help to minimize worker exposure to nanomaterials. Examples of good practices include the following:

Work areas should be cleaned at the end of each work shift (at a minimum) using either a HEPA-filtered vacuum cleaner or wet wiping methods. Dry sweeping or air hoses should not be used to clean work areas. Cleanup should be conducted in a manner that prevents worker contact with wastes; the disposal of all waste material should comply with all applicable Federal and State, and local regulations.

The storage and consumption of food or beverages in workplaces should be prevented where nanomaterials are handled.

Hand-washing facilities should be provided and workers encouraged using them before eating, smoking, or leaving the worksite.

Facilities for showering and changing clothes should be provided to prevent the inadvertent contamination of other areas (including take-home) caused by the transfer of nanoparticles on clothing and skin.

C. Personal Protective Clothing

Currently, no guidelines are available on the selection of clothing or other apparel for the prevention of dermal exposure to nanoparticles. Published research has shown that penetration efficiencies for 8 widely different fabrics (including woven, non-woven, and laminated fabrics) against 0.477 μm particles range from 0.0 % to 31%, with an average of 12% [Shalev et al. 2000]. Penetration efficiencies for nanoparticles have not been studied. However, even for powders in the macro scale, it is recognized that skin protective equipment (i.e. suits, gloves and other items of protective clothing) is very limited in its effectiveness to reduce or control dermal exposure [Schneider et al. 2000]. In any case, although nanoparticles may penetrate the epidermis, there has been little work to suggest that penetration leads to disease; and no dermal exposure standards have been proposed.

Some existing clothing standards already incorporate testing with nanometer-sized particles, and therefore provide some indication of the effectiveness of protective clothing to nanoparticles. For instance, ASTM standard F1671–03 specifies the use of a 27 nm bacteriophage to evaluate the resistance of materials used in protective clothing from the penetration of bloodborne pathogens [ASTM Subcommittee F23.40 2003].

NIOSH plans to conduct laboratory research on test methods to determine particle penetration through fabrics used into protective clothing and ensembles. As results from this research become available, they will be posted to the NIOSH website.

D. Respirators

The use of respirators is often required when engineering and administrative controls do not adequately keep worker exposures to an airborne contaminant below a regulatory limit or an internal control target. Currently, there are no specific exposure limits for airborne exposures to engineered nanoparticles although occupational exposure limits and guidelines (e.g., OSHA, NIOSH, ACGIH) exist for larger particles of similar chemical composition. Current scientific evidence indicates that nanoparticles may be more biologically reactive than larger particles of similar chemical composition and thus may pose a greater health risk when inhaled. In determining the effectiveness of controls or the need for respirators, it would therefore be prudent to consider both the current exposure limits or guidelines (e.g., PELs, RELs, TLVs) and the increase in surface area of the nanoparticles relative to that of particles for which the exposure limits or guides were developed.

The decision to institute respiratory protection should be based on a combination of professional judgment and the results of the hazard assessment and risk management practices recommended in this document. The effectiveness of administrative, work practice, and engineering controls can be evaluated using the measurement techniques described in *Exposure Assessment and Characterization*. If worker airborne exposure to nanoparticles remains a concern after instituting measures to control exposure, the use of respirators can further reduce worker exposures. Several classes of respirators exist that can provide different levels of protection when properly fit tested on the worker. Table 1 lists various types of particulate respirators that can be used; information is also provided on the level of exposure reduction that can be expected from each and the advantages and disadvantages of each respirator type. To assist respirator users, NIOSH has published the document *NIOSH Respirator Selection Logic (RSL)* that provides a process that respirator program administrators can use to select appropriate respirators (see www.cdc.gov/niosh/docs/2005-100/default.html). As new toxicity data for individual nanomaterials become available, NIOSH will review the data and make recommendations for respirator protection. When respirators are required to be used in the workplace, the Occupational Safety and Health Administration (OSHA) respiratory protection standard [29 CFR* 1910.134] requires that a respiratory program be established that includes the following program elements: (1) an evaluation of the worker's ability to perform the work while wearing a respirator, (2) regular training of personnel, (3) periodic environmental monitoring, (4) respirator fit testing, and (5) respirator maintenance, inspection, cleaning, and storage. The standard also requires that the selection of respirators be made by a person knowledgeable about the workplace and the limitations associated with each type of respirator. OSHA has also issued guidelines for employers who choose to establish the voluntary use of respirators [29 CFR 1910.134 Appendix D].

*Code of Federal Regulations. See CFR in references.

Table 1 lists the NIOSH assigned protection factors (APF) for various classes of respirators. The APF is defined as the minimum anticipated protection provided by a properly functioning respirator or class of respirators to a given percentage of properly fitted and trained users. The APF values developed by NIOSH are based in part on laboratory studies and take into consideration a variety of factors including the inward leakage caused by penetration through the filter and leakage around the face seal of the respirator. NIOSH is not aware of any data specific to the face seal leakage of nanoparticles. Numerous studies have been conducted on larger particles and on gases/vapors. For example, work done by researchers at the U.S. Army RDECOM on a head-form showed that mask leakage (i.e., simulated respirator fit factor) measured using submicron aerosol challenges (0.72 μm polystyrene latex spheres) was representative of vapor challenges such as sulfur hexafluoride (SF_6) and isoamyl acetate (IAA) [Gardner et al, 2004]. NIOSH plans to conduct a laboratory study to determine whether nanoparticle face seal leakage is consistent with the leakage seen by larger particles and gases/vapors. As results from this research become available, they will be posted to the NIOSH website.

NIOSH tests and certifies the filtration performance of air purifying respirators. One NIOSH certification test uses a polydisperse distribution of NaCl particles with a count median diameter (CMD) of 0.075 +/− 0.020 μm and a geometric standard deviation (GSD) of less than 1.86 for N- designated respirators [NIOSH, 2005a]. For R- and P- designated respirators, NIOSH tests using a polydisperse distribution of dioctyl phthalate (DOP) particles with a CMD of 0.185 +/− 0.020 μm and a GSD of less than 1.60 [NIOSH, 2005b]. For the lognormal distribution of NaCl aerosols used in the certification test, a broad range of particle sizes (e.g., 95% of the particles lie in the range of 22 nm – 259 nm) with a mass median diameter (MMD) of about 0.24 μm (or 240 nm) is used to determine whether the respirator filter performance is at least 95%, 99%, or 99.97% efficient. All of the particles penetrating through the filter are measured simultaneously using a forward light scattering photometer. According to single fiber filtration theory, particles larger than 0.3 μm are collected most efficiently by impaction, interception, and gravitational settling, while particles smaller than 0.3 μm are collected most efficiently by diffusion or electrostatic attraction [Hinds 1999]. Penetration of approximately 0.3 μm particles represents the worst case because these particles are considered to be in the range of the most penetrating particle size [Stevens and Moyer 1989, TSI 2005; NIOSH 1996]. However, the most penetrating particle size range for a given respirator can vary based on the type of filter media employed and the condition of the respirator. For example, the most penetrating particle size for N95 respirators containing electrostatically charged filter media can range from 50–100 nm [Martin and Moyer, 2000; Richardson et al, 2005] to 30–70 nm [Balazy et al, 2006].

According to single fiber filtration theory, below the most penetrating particle size, filtration efficiency will increase as particle size decreases. This trend will continue until the particles are so small that they behave like vapor molecules. As particles approach molecular size, they may be subject to thermal rebound theory, in which particles literally bounce through a filter. As a result, particle penetration will increase. The exact size at which thermal rebound will occur has not been reported in the literature. However, a recent study by Heim et al [2005] found that there was no discernable deviation from classical single-fiber theory for particles as small as 2.5 nm diameter. NIOSH recently funded a contract with the University of Minnesota to study the collection efficiency of respirator filter media for particles in the 3–100 nm range. In this study, the researchers observed that penetration of nanoparticles through filter media decreased down to 3 nm as expected by traditional filtration theory [Pui and Kim, 2006]. No evidence for thermal rebound of nanoparticles in the size ranges studied was found. Based on these preliminary findings, NIOSH certified respirators should provide the expected levels of protection if properly selected and fit tested as part of a complete respiratory protection program. NIOSH plans to continue studying the nanoparticle collection efficiency of NIOSH certified respirators to validate these findings. As results from this research become available, they will be posted to the NIOSH website.

E. Cleanup and Disposal of Nanomaterials

No specific guidance is currently available on cleaning up nanomaterial spills or contaminated surfaces. Until relevant information is available, it would be prudent to base strategies for dealing with spills and contaminated surfaces on current good practices, together with available information on exposure risks and the relative importance of different exposure routes. Standard approaches to cleaning up powder and liquid spills include the use of HEPA-filtered vacuum cleaners, wetting powders down, using dampened cloths to wipe up powders and applying absorbent materials/liquid traps.

Damp cleaning methods with soaps or cleaning oils is preferred. Cleaning cloths should be properly disposed. Drying and reuse of contaminated cloths can result in re-dispersion of particles. Use of commercially available wet or electrostatic microfiber cleaning cloths may also be effective in removing particles from surfaces with minimal dispersion into the air.

Energetic cleaning methods such as dry sweeping or the use of compressed air should be

Table 1. Air-purifying particulate respirators

Respirator type	NIOSH assigned protection factor [106]	Advantages	Disadvantages	Cost (2004 dollars)
Filtering facepiece (disposable)	10	– Lightweight – No maintenance or cleaning needed – No effect on mobility	– Provides no eye protection – Can add to heat burden – Inward leakage at gaps in face seal – Some do not have adjustable head straps – Difficult for a user to do a seal check – Level of protection varies greatly among models – Communication may be difficult – Fit testing required to select proper facepiece size – Some eyewear may interfere with the fit – Respirator must be replaced whenever it is soiled, damaged or has noticeably increased breathing resistance.	$0.70 to $10

(Continued)

Table 1 (Continued). Air-purifying particulate respirators

Respirator type	NIOSH assigned protection factor [106]	Advantages	Disadvantages	Cost (2004 dollars)
Elastomeric half-facepiece	10	– Low maintenance – Reusable facepiece and replaceable filters and cartridges – No effect on mobility	– Provides no eye protection – Can add to heat burden – Inward leakage at gaps in face seal – Communication may be difficult – Fit testing required to select proper facepiece size – Some eyewear may interfere with the fit	Facepiece: $12 to $35 Filters: $4 to $8 each
Powered with loose-fitting facepiece	25	– Provides eye protection – Protection for people with beards, missing dentures or facial scars – Low breathing resistance – Flowing air creates cooling effect – Face seal leakage is generally outward – Fit testing is not required – Prescription glasses can be worn	– Added weight of battery and blower – Awkward for some tasks – Battery requires charging – Air flow must be tested with flow device before use	Unit: $400 to $1,000 Filters: $10 to $30

(Continued)

Table 1 (Continued). Air-purifying particulate respirators

Respirator type	NIOSH assigned protection factor [106]	Advantages	Disadvantages	Cost (2004 dollars)
Powered with loose-fitting facepiece (Continued)		– Communication less difficult than with elastomeric half-facepiece or full-facepiece respirators – Reusable components and replaceable filters		
Elastomeric full-facepiece with N-100, R-100, or P-100 filters	50	– Provides eye protection – Low maintenance – Reusable facepiece and replaceable filters and cartridges – No effect on mobility – More effective face seal than that of filtering facepiece or elastomeric half-facepiece respirators	– Can add to heat burden – Diminished field-of-vision compared to half-facepiece – Inward leakage at gaps in face seal – Fit testing required to select proper facepiece size – Facepiece lens can fog without nose cup or lens treatment – Spectacle kit needed for people who wear corrective glasses	Facepiece: $90 to $240 Filters: $4 to $8 each Nose cup: $30

(Continued)

Table 1 (Continued). Air-purifying particulate respirators

Respirator type	NIOSH assigned protection factor (106)	Advantages	Disadvantages	Cost (2004 dollars)
Powered with tight-fitting half-facepiece or full-facepiece	50	– Provides eye protection with full-facepiece – Low breathing resistance – Face seal leakage is generally outward – Flowing air creates cooling effect – Reusable components and replaceable filters	– Added weight of battery and blower – Awkward for some tasks – No eye protection with half-facepiece – Fit testing required to select proper facepiece size – Battery requires charging – Communication may be difficult – Spectacle kit needed for people who wear corrective glasses with full face-piece respirators – Air flow must be tested with flow device before use	Unit: $500 to $1,000 Filters: $10 to $30

Note: The assigned protection factors in this table are from the NIOSH Respirator Selection Logic [NIOSH 2004]. When the table was prepared, OSHA had proposed amending the respiratory protection standard to incorporate assigned protection factors. The Internet sites of NIOSH (www.cdc.gov/niosh) and OSHA (www.osha.gov) should be periodically checked for the current assigned protection factor values.

avoided or only be used with precautions that assure that particles suspended by the cleaning action are trapped by HEPA filters. If vacuum cleaning is employed, care should be taken that HEPA filters are installed properly and bags and filters changed according to manufacturer's recommendations.

While vacuum cleaning may prove to be effective for many applications, the following issues should be considered. Forces of attraction may make it difficult to entrain particles off surfaces with a vacuum cleaner. The electrostatic charge on particles will cause them to be attracted to oppositely charge surfaces and repelled by similarly charged surfaces. An oppositely charged vacuum brush or tool may repel particles, making it difficult to capture the aerosol or even causing it to be further dispersed. Vigorous scrubbing with a vacuum brush or tool or even the friction from high flow rates of material or air on the vacuum hose can generate a charge. The vacuum cleaners recommended for cleaning copier and printer toners have electrostatic-charge-neutralization features to address these issues.

When developing procedures for cleaning up nanomaterial spills or contaminated surfaces, consideration should be given to the potential for exposure during cleanup. Inhalation exposure and dermal exposure will likely present the greatest risks. Consideration will therefore need to be given to appropriate levels of personal protective equipment. Inhalation exposure in particular will be influenced by the likelihood of material re-aerosolization. In this context, it is likely that a hierarchy of potential exposures will exist, with dusts presenting a greater inhalation exposure potential than liquids, and liquids in turn presenting a greater potential risk than encapsulated or immobilized nanomaterials and structures.

As in the case of any material spill or cleaning of contaminated surfaces, handling and disposal of the waste material should follow exiting Federal, State, or local regulations.

Occupational Health Surveillance

The unique physical and chemical properties of nanomaterials, the increasing growth of nanotechnology in the workplace, and information suggesting that engineered nanoscale materials may pose a health and safety hazard to workers all underscore the need for medical and hazard surveillance for nanotechnology. Every workplace dealing with nanoparticles, engineered nanomaterials, or other aspects of nanotechnology should consider the need for an occupational health surveillance program. NIOSH is in the process of formulating guidance relevant to occupational health surveillance for nanotechnology. The intent of the guidance is to provide a framework for utilizing existing medical and hazard surveillance mechanisms to create occupational health surveillance programs for nanotechnology workers. The NIOSH guidance will not be a proscriptive set of recommendations for a specific type of surveillance program, but rather will provide information that can be used to create appropriate occupational health surveillance to fit the needs of workers and organizations involved with nanotechnology. The framework will present information to help initiate occupational health surveillance where none exists. It is likely that, as the field of nanotechnology changes over time, continual reassessment of potential hazards and exposures will be required to initiate and maintain an effective surveillance program.

Research

NIOSH has developed a strategic plan for research on the occupational safety and health aspects of nanotechnology. The plan is available at www.cdc.gov/niosh/topics/nanotech/strat_plan.html. Review and feedback on the plan is welcomed.

Critical Research Topics

NIOSH has focused its research efforts in the following 10 critical topic areas to guide in addressing knowledge gaps, developing strategies, and providing recommendations.

- **Toxicity:** Investigating and determining the physical and chemical properties (ex: size, shape, solubility) that influence the potential toxicity of nanoparticles; evaluating short and long-term effects that nanomaterials may have in organ systems and tissues (ex: lungs); determining biological mechanisms for potential toxic effects; creating and integrating models to assist in assessing possible hazards; and determining if a measure other than mass is more appropriate for determining toxicity.
- **Epidemiology and Surveillance:** Evaluating existing epidemiological workplace studies where nanomaterials are used; identifying knowledge gaps where epidemiological studies could advance understanding of nanomaterials and evaluating the likelihood of conducting new studies; integrating nanotechnology health and safety issues into existing hazard surveillance methods and determining whether additional screening methods are needed; and using existing systems to share data and information about nanotechnology.
- **Risk Assessment:** Determining the likelihood that current exposure-response data (human or animal) could be used in identifying and assessing potential occupational hazards; and developing a framework for evaluating potential hazards and predicting potential occupational exposure to nanomaterials.
- **Measurement Methods:** Evaluating methods of measuring mass of respirable particles in the air and determining if this measurement can be used to measure nanomaterials; developing and field-testing practical methods to accurately measure airborne nanomaterials in the workplace; and developing testing and evaluation systems to compare and validate sampling instruments.
- **Exposure and Dose:** Determining key factors that influence the production, dispersion, accumulation, and re-entry of nanomaterials into the workplace; assessing possible exposure when nanomaterials are inhaled or settle on the skin; determining how possible exposures differ by work process; and determining what happens to nanomaterials once they enter the body.
- **Controls:** Evaluating the effectiveness of engineering controls in protecting workers from nanoaerosols and developing new controls in reducing occupational exposures to nanoaerosols and developing new controls where needed; evaluating and improving current personal protective equipment; developing recommendations to prevent or limit occupational exposures from nanoaersols (ex: respirator fit testing); evaluating suitability of control banding techniques where additional information is needed; and evaluating the effectiveness of alternative materials.

- **Safety:** Identifying current work practices that do not provide adequate precautions against exposures; and recommending alternative work practices to eliminate or reduce workplace exposures.
- **Communication and Education:** Establishing partnerships to allow for identification and sharing of research needs, approaches, and results; and developing and disseminating training and educational materials to workers and health and safety professionals.
- **Recommendations and Guidance:** Using the best available science to make interim recommendations for workplace safety and health practices during the production and use of nanomaterials. Evaluating and updating occupational exposure limits for mass-based airborne particles to ensure good continuing precautionary practices.
- **Applications:** Identifying uses of nanotechnology for application in occupational safety and health; and evaluating and disseminating effective applications to workers and occupational safety and health professionals.

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