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Biosafety, Occupational Health and Nanotechnology

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Abstract

Nanotechnology promises to improve the quality of human life, but it has also provoked concerns about potential adverse health effects on workers, the environment and consumers. Effective risk assessment and risk management of nanotechnology requires: 1) knowing how engineered nanoscale particles (NPs) can gain entry into the human body (routes of exposure); 2) knowing whether engineered NPs can migrate from their point of entry to other locations in the body (translocation); 3) determining what adverse biological effects may occur in response to engineered NP exposure (toxicity); 4) knowing which measurement of exposure and dose correlates best to toxicity (exposure and dose metrics); and 5) knowing how best to monitor exposed populations to detect the occurrence of any adverse health effects (health surveillance). This article reviews what is currently known about potential health risks to workers from exposure to engineered NPs, as well as the best methods to control those risks, in order to ensure that their use in the laboratory and industry conforms to the best principles of occupational health and biosafety.

Introduction

Nanotechnology refers to a new set of technologies that are used to develop nanometer-sized structures and devices (<100 nanometers in at least one dimension) with unique, or enhanced properties for commercial application (NSTC, 2004). At the nanometer scale, certain materials exhibit new properties not exhibited at the macro scale. For instance, materials that were not reactive at the macro scale become highly reactive at the nanoscale

largely because of their greatly increased surface area. New size-dependent properties of carbon and various metals represent both the promise of nanotechnology as well as the concern about potential adverse health effects on workers, the environment and consumers.

Nanotechnology's promise to dramatically improve our quality of life has attracted significant worldwide investment from both private and public sources. Nanotechnology applications are coming to market rapidly; the worldwide nano product market is estimated to reach $1 trillion dollars by 2015 (Roco, 2005). In 2005, nearly $10 billion dollars were spent on nanotechnology research and development alone (Holman et al., 2006). Over 300 nanotechnology-based products are already in commerce, including over 70 healthcare related products (WWICS, 2006). Nanotechnology-enabled applications in medical imaging, diagnosis, drug delivery and anticancer therapy offer exciting new possibilities for significantly advancing medical science in the 21st century (Vogel & Baird, 2005). Hand-in-hand with nanotechnology's promise to deliver materials with unique and useful properties, there also comes a big challenge. How can nanotechnology and its commercial products be proactively developed, while at the same time minimizing any potential risks to human health?

In 2004, the National Institute for Occupational Safety and Health (NIOSH) established a Nanotechnology Research Center to identify the risk implications of nanotechnology for worker health, and to devise ways to protect workers from any identified adverse health effects from working with nanomaterials. NIOSH's research efforts reflect the widespread desire to identify health implications from nanotechnology early in its development, before irreversible harm can occur and to recommend control measures to prevent societal harm we have seen from previous commercial products like asbestos.

Concerns about the occupational, environmental and consumer health implications of nanotechnology have come from a number of different sources. Environmental groups such as the Action Group on Erosion, Technology and Concentration (ETC), the insurance industry, professional scientific associations and academic researchers have all published reports calling for more attention and resources devoted to identifying any risks from nanotechnology (Maynard et al., 2006). Given the current modest investment in nanotechnology hazard identification, risk characterization and risk assessment, it is not surprising then that a lack of information exists about the human health effects stemming from the novel properties of nanomaterials, the great variability found among various nanostructures, and the wide range of chemical composition of nanomaterials (NSTC, 2006). In addition to the societal damage that actual risks can produce, perceived risks can also affect how broadly a new technology is accepted by the public. It is crucial then that nanotechnology's risks, both actual and perceived, be identified swiftly and managed responsibly if the promise of nanotechnology is to be realized.

Effective risk assessment, risk characterization and risk management of nanotechnology requires: 1) knowing how engineered nanoscale particles (NPs) gain entry into the human body (routes of exposure); 2) knowing whether engineered NPs can migrate from their point of entry to other locations in the body (translocation); 3) determining what adverse biologic effects may occur in response to engineered NP exposure (toxicity); 4) knowing which measurement of exposure and dose correlates best to toxicity (exposure and dose metrics); and 5) knowing how to best monitor exposed populations to detect the occurrence of any adverse health effects (health surveillance).

At the present time, we are just beginning to develop answers to these important questions that will help us develop effective risk management for engineered NPs. We do have substantial information about other NPs, which have been incidentally generated by anthropogenic processes involving industrial processes, combustion, welding, automobile and diesel engines operation (incidental NPs); created by natural processes such as volcanic activity, or synthesized by living systems, such as proteins and viruses (natural NPs).

Drawing upon our knowledge of routes of exposure, toxicity and health effects seen from human exposure to incidental NPs, we review in this article what is currently known about the potential health risks to workers from exposure to engineered NPs and the best available methods to control those risks in order to ensure their use in the laboratory and in industry conforms to the best principles of occupational health and biosafety.

Routes of Exposure

Inhalation

The most common route of exposure to any aerosol particle in the workplace, including a NP, is through inhalation. In this route, the deposition of NPs in the respiratory tract is determined by the aerodynamic diameter of a stand-alone particle, or of a NP agglomerate, in which many weakly attached discrete NPs form a particle larger than 100 nm. However, agglomerates have the potential to deagglomerate during, or after deposition in the respiratory tract. Discrete NPs are deposited in all regions of the lung, including the deep alveolar region, to a greater extent than larger respirable particles (ICRP, 1994). Deposition increases with exercise due to an increase in breathing rate and a change from nasal-to-mouth breathing (Jaques & Kim, 2000; Daigle et al., 2003). Deposition also increases among persons with existing lung diseases, or conditions (Brown et al., 2002). Based on animal studies, discrete NPs may enter the bloodstream from the lungs and translocate to other organs (Takenaka et al., 2001; Nemmar et al., 2002; Oberdörster et al., 2002).

Inhalational exposure is also an important route for contracting viral diseases such as influenza. It is believed that in this route of exposure, viruses are carried in a liquid-matrix of sub-micron particles called droplet nuclei, which are generated by expiration, coughing, and sneezing. This route is also employed for intentional exposure to attenuated viruses mimicking the natural route of influenza infection in some nasal-spray vaccines against influenza (Maassab et al., 1990). The respiratory route is also under active investigation as a potential route of drug delivery using engineered NPs. Coupling of drug molecules with carrier-NPs may allow controlled deposition rates via inhalation route and facilitate translocation to the blood stream (Vogel & Baird, 2005).

Ingestion

Ingestion may also accompany inhalation exposure, because particles that are cleared from the respiratory tract via the mucociliary escalator may be swallowed (ICRP, 1994). In addition, engineered NPs can enter the digestive tract by ingestion of contaminated food or water and by hand-to-mouth transfer from contaminated surfaces. The ability of mucosal membranes and the gastrointestinal tract to absorb and, in some cases, facilitate systemic distribution of NPs, such as liposomes, proteins and viruses (e.g., rotavirus, hepatitis E) is well-known. In addition, it has been shown that inorganic particles, such as 500 nanometer (nm) titanium dioxide (Jani et al., 1994) and nanoscale gold (Hillyer, 2001), have the potential to cross the digestive tract lining and translocate to systemic organs such the liver, spleen, lung and peritoneal tissues. There is also evidence that smaller particles can be transferred more readily than their larger counterparts across the intestinal wall (Behrens et al., 2002). These natural processes are presently under investigation for potential applications in developing nanoscale vehicles for oral drug and nutrients delivery: poly(DL-lactide-co-glycolide)-coated particles (Brayden & Baird, 2001), liposomes (Hussain et al., 2001), fatty acid polymer particles (Mathiowitz et al., 1997), and virosomes (Rae et al., 2005). Such nanoscale formulations have the potential to improve the solubility of poorly soluble drugs by enveloping them into an amphyphilic coating; the permeability through bioconjugation with polymers facilitating trans- and para-cellular transfer and through nanoscale size and morphology, which could be recognized and absorbed by intestinal cells; and the stability through controlled degradation, adhesion to intestinal mucosa and availability of intestinal enzymatic inhibitors. For example, intact, biologically active insulin and pancreatic ribonuclease can be delivered into the blood circulation through oral administration in the presence of bile acid and protease inhibitor (Ziv et al., 1987).

Dermal

Dermal exposure can be another route for NPs to gain entry into the human body. Penetration of intact skin can occur through a number of pathways, including sweat ducts, stratum corneum via inter- or intracellular modes and hair follicles. The ability of nanoscale particles to cross the skin's outer layer of stratum corneum remains a subject of intense study and debate. Some studies indicate that particles as large as 1000 nm can penetrate human skin upon flexing in vitro (Tinkle, 2003), while other studies show that nanoscale titanium dioxide remained on the outermost layer of unperturbed human skin in vivo after six hours with none detected in the deeper stratum corneum, epidermis or dermis (Schulz et al., 2002). A recent study showed that mechanical flexing of skin can increase the rate and the amount at which fullerene-based amino acid engineered NPs can penetrate through the skin (Rouse et al., 2007).

From biological examples, it is well known that only small lipophilic molecules can penetrate skin, while proteins are believed to be unable to pass through this tough barrier. Physical approaches, including electric fields, ultrasound, jet injectors, micro-needles and thermal ablation have been shown to aid in breaching the skin barrier (Prausnitz, 2006). Recently, transdermal delivery of intact, biologically active protein medications such as insulin has been shown possible in the presence of phage peptide chaperones (Chen et al., 2006). It appears that the mechanism of penetration is not specific to insulin and involves interactions between phage peptide and the skin facilitating transfollicular route of insulin transport across the skin.

A number of viruses, such as the herpes virus, are known to cross the skin and mucosal barrier by entering nerve endings and translocating via an axoplasmic route to the neuronal soma ending in the brain. Similarly, animal studies have shown that discrete insoluble NPs, from 20 to 500 nm diameter, deposited in the nasal region may be able to enter the brain by translocation along the sensory nerves, including olfactory and trigeminal nerves (Oberdörster et al., 2004; Oberdörster et al., 2005; De Lorenzo, 1970; Adams & Bray, 1983; Hunter & Dey, 1998).

Parenteral

NPs can be also introduced into human bodies via the parenteral route either incidentally through cuts and other damage to intact skin, or intentionally for drug delivery, medical imaging, or other applications. Engineered NPs for drug applications can deliver markedly improved characteristics: 1) enhanced solubility especially for hydrophobic entities; 2) increased stability through coatings capable of avoiding the immune system; 3) improved specificity through multifunctional capabilities and active and passive targeting; and 4) the enhanced ability to penetrate specific barriers like the blood-brain barrier. Engineered NPs that enter the body parenterally can interact with plasma proteins in trivial ways, such as covalently bonding to proteins without changing the function of the protein, and non-trivially, by interacting

with the body's systems similar to interactions characteristic of certain natural nanoscale particles, such as proteins and viruses.

Translocation of Nanoparticles

Deagglomeration, translocation, and distribution play key roles in the fate of NPs once they gain entrance into the human body. NPs, which are smaller than 20 nm, can transit through blood vessel walls. Magnetic nanoparticles, for instance, can image metastatic lesions in lymph nodes, because of their ability to exit the systemic circulation through the permeable vascular epithelium (Bogdanov et al., 2005). Some NPs can also penetrate the blood-brain barrier through paracellular movement, passive diffusion, transport and endocytosis (Lockman et al., 2003; Kreuter, 2004). Translocated NPs can become biopersistent in the body if the immune system fails to recognize them as foreign bodies, or they can potentially be cleared from the body because of biodegradation, or their higher solubility compared to larger sized particles of the same chemistry (Borm et al., 2006).

Toxicity of Nanoparticles

Incidental NPs

The results of animal and human studies on exposure and response to incidental NPs, or other respirable particles, provide a basis for preliminary estimates of the possible adverse health effects from exposures to engineered NPs (Gwinn & Vallyathan, 2006). Perhaps the most important study to be conducted in the last 10 years has shown a link between exposure to a high level of urban air pollution, including incidental NPs, and increased morbidity and mortality due to cardiovascular disease (Pope et al., 2004). More specifically, a correlation was found between number concentration of incidental NPs in the ambient air and blood biomarkers of inflammation and endothelial dysfunction and coagulation among patients with coronary heart disease (Rückerl et al., 2006). Other examples of observed correlations between exposures to incidental NPs and adverse health effects include: exposures to diesel exhaust particulate have been correlated with an elevated risk of lung cancer (Steenland et al., 1998; Garshick et al., 2004), while exposures to welding fumes have been found to cause respiratory effects, such as bronchitis, airway irritation, lung function changes, and a possible increase in the incidence of lung cancer (Antonini, 2003). Occupational exposure to nanometer-sized polytetrafluoroethylene (PTFE) fume (generated at temperatures more than 425 degrees centigrade) 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 due to agglomeration and to changes in surface chemistry (Johnston et al., 2000; Oberdörster et al., 2005). Human case studies have reported pulmonary edema in workers exposed to PTFE fume, and an accidental death in a worker when equipment malfunctioned, caused overheating of the PTFE resin and release of the PTFE pyrolysis products in the workplace (Lee et al., 1997). While incidentally-generated PTFE fume differs from engineered NPs, these studies illustrate the size-dependent properties and surface activity of NPs that may be associated with an acute toxic hazard.

Engineered NPs

When it comes to evaluating the health effects of natural nanoscale materials synthesized by living organisms, a wide range of responses exist from the benign and beneficial, such as those to insulin and growth hormone, to the adverse and even lethal effects from protein biotoxins. Similarly, engineered nanoscale materials can potentially elicit the full range of health responses observed for natural and incidental nanoscale materials. Some of these responses could be also used for beneficial medical applications. For example, a recent report describes a non-toxic and non-immunogenic liquid containing self-assembling peptides, which form a nanofiber barrier stopping bleeding within 15 seconds of application to a wound (Ellis-Behnke et al., 2006).

A single-walled carbon nanotube (SWCNT) is an example of engineered nanoscale material whose toxicological properties have been studied extensively. For example, the National Institute for Occupational Safety and Health (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 and oxidative stress, decreased pulmonary function, decreased bacterial clearance and the early onset of progressive, interstitial fibrosis. Deposition of agglomerates resulted in the development of granulomas, while deposition of more dispersed nanotube structures resulted in the rapid development of interstitial fibrosis within seven days, which progressed over a 60-day post-exposure period. SWCNT was found to be more fibrogenic than an equal mass of either ultrafine carbon black or fine quartz.

Descriptors of Nanoparticle Toxicity

A number of reviews on the health effects of NPs have highlighted the unique features of NPs, which distinguish them from either conventional molecular species, or larger particles of bulk materials (Ostiguy et al., 2006; Nel et al., 2006; NSTC, 2006). The three features—size, surface, and shape—discussed below, either separately, or in combination, may ultimately be shown in

the future to predict the toxicity of NPs.

Size. Due to their small size, NPs can cross cell membranes and penetrate blood vessel walls and the blood-brain barrier via passive and active diffusion and interfere with cellular functions (Geiser et al., 2005).

In addition, if the toxic properties of particles are determined by interactions occurring at the interface between particles and biological systems, then toxic response should increase as particle size decreases for the same mass dose. Such a dependence was observed for a number of poorly soluble low toxicity materials (Oberdörster, 2000).

Surface. For the same mass of any particular material, the combined surface area of a particle is inversely proportional to particle size. If the toxic properties of particles are determined by interactions occurring at the interface between particles and biological systems, then toxic response should correlate with the total surface area of particles. Indeed, it was observed in animal studies that the inflammatory response to inhaled TiO_2 particulates of different sizes, including those at the nanoscale size range, varied as a function of surface area (Oberdörster, 2000).

As particle size decreases, the fraction of atoms on the surface of the particle increases. This change becomes more pronounced for particles smaller than 100 nm in diameter with more than 1% of atoms on the surface and increases to 50% for 1 nm particles. Thus, surface characteristics, such as surface atomic and electronic structure and redox activity, become critical for nanoscale materials. Yet, toxic properties can be modulated by modifying the chemistry of the particle surface (Sayes et al., 2004). An example of this also comes from microbiology where surface chemistry plays a crucial role in the mechanism of viral infection. Receptor proteins expressed on the viral surface provide a mechanism for viral attachment to cellular membrane proteins of cells under attack. A slight modification of proteins expressed on the viral surface dramatically increases their virulence, or renders them innocuous (Wiley & Skehel, 1987).

Shape. One of the benefits of nanotechnology is the ability to control material structure with atomic precision. This control of materials on a nanoscale results in our ability to generate an immense number of engineered NPs with different shapes. Examples of the simplest engineered NPs are spheres, tubes, wires, rods, belts, and flakes. Examples of the more complex engineered NPs are tripods, flowers and brushes. Finally, the most complex NPs are three-dimensional structures such as multifunctional nanoscale particles like functionalized liposomes, virosomes and dendrimers.

Nanotubes and nanowires are shapes other than roughly spherical for which toxicological properties have been studied to some degree. Shape may be an important factor in toxicity as it has been shown that long carbon nanotubes cannot be engulfed by macrophages (Stone & Donaldson, 2006).

Properties of the core of nanoscale materials could also have effects on toxicological properties. For example, the electronic structure of the core could modulate reduction-oxidation type reactions on the particle surface. The chemical structure of the core could also become exposed during biodegradation and dissolution processes, and could exert toxicological effects distinct from those of the surface layer.

Exposure and Dose Metrics

Historically, a mass-based paradigm has been employed by industrial hygienists to assess worker exposure to airborne particulates. The exposure and dose metrics for engineered NPs in the workplace are now under active study because NPs have such little mass to measure. Since NPs have little mass, a new exposure and dose metrics may be needed. Currently, particle number and particle surface area are being studied as an exposure and dose metric.

An exposure and dose metric for engineered nanoscale materials, which have a range of either chemical compositions, or structures, or both, will depend on the mechanism of their toxicological and pharmacokinetic behavior. For example, poorly soluble low-toxicity particles, which interact with biological systems at the particle surface, can have their exposure and dose expressed as combined surface area. Thus, experimental studies in rodents and cell cultures have shown that the toxicity of nanoscale particles is greater than that of the same mass of larger particles of a similar chemical composition, and surface area correlates best with the observed toxicological responses (Oberdörster et al., 1994; Tran et al., 2000).

In addition to particle surface area, other particle characteristics may influence the toxicity, including solubility, shape, and surface chemistry (Oberdörster et al. 2005; Maynard & Kuempel, 2005). For nanoscale particles, which quickly disintegrate upon interaction with biological systems through dissolution or degradation (for example, water-soluble salts or quickly bio-degrading organic oligomeric particles), a mass-based metric could be sufficient to characterize exposure and dose. Using an analogy with asbestos and other mineral fibers for which fiber-count-based occupational exposure limits are used, an exposure and dose metric for fibers with diameters in the nanoscale range expressed as the number of fibers administered to the living system should be considered (NIOSH, 1997).

Occupational Health Surveillance

The unique physical and chemical properties of engineered nanomaterials, the increasing growth of nanotechnology in the workplace, and information suggesting that

engineered nanoscale materials may pose a health hazard to workers, all underscore the need for surveillance of exposed populations for adverse health effects. Existing medical and hazard surveillance mechanisms can be considered in designing site-specific occupational health surveillance programs for nanotechnology workers (Baker & Matte, 1994). It is likely that as the field of nanotechnology evolves over time, continual reassessment of potential hazards and exposures will be required to initiate and maintain an effective surveillance program. NIOSH is currently engaged in identifying the issues involved in occupational health surveillance for workers in nanotechnology research and development centers as well as those engaged in nanomanufacturing on the commercial level.

Risk Assessment

Risk assessment is a fundamental component of evaluating the occupational health risks of nanomaterials, and is the basis for effective risk management decisions (Herber et al., 2001). Quantitative risk assessment allows for a comparison between actual workplace exposure and a health risk-based occupational exposure limit (OEL). An example of quantitative risk assessment analysis for nanoscale particles can be found in the draft *NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide* (NIOSH, 2005). This document establishes a draft recommended exposure limit (REL) for *nanoscale* titanium dioxide (TiO_2) at 0.1 mg/m^3 as a time-weighted average concentration for up to 10 hr/day during a 40-hour work week, which is 15 times lower than the draft recommended exposure limit in the same document for *macroscale* TiO_2.

In the absence of adequate dose-response data for specific engineered nanoscale materials, qualitative risk assessment approaches can be used. Qualitative risk assessment can be based on comparisons between engineered nanoscale particles and incidental NPs, or to larger respirable particles, or fibers of similar chemical composition. An example of the qualitative risk assessment approach is contained in NIOSH's web-based *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH,* which we encourage readers to consult for current NIOSH risk management recommendations (NIOSH, 2006).

Given the paucity of data for a wide range of nanoscale materials, which are being used now in industry or in research laboratories, regulatory OELs, such as an OSHA mandatory permissible exposure limit (PEL), are unlikely to be promulgated for some time. Therefore, industry-based, or laboratory-based OELs could be established to facilitate development of a site-specific industrial hygiene program. Generic procedures to establish industry-based OELs were first developed by the pharmaceutical industry years ago and include the following steps: 1) evaluation of available animal, bioavailability and pharmacokinetic data; 2) supplemental studies to evaluate any health effects resulting from occupationally specific exposures, such as through dermal and inhalational exposures; 3) calculation of "no observed adverse effect level" or "the lower effective dose" in the benchmark dose method using the most sensitive occupationally relevant adverse effect; and 4) correction of this level for body weight, volume of air breathed during a typical workday (for inhalation route of exposures), and the uncertainty factor accounting for inter-individual variability and interspecies extrapolation (Agius, 1989; Naumann et al., 1996).

Physical factors affecting materials dispersion, such as volatility for liquid formulations and dustiness for dry formulations, also need to be considered when conducting risk assessments. While volatility can be more easily estimated using a well-established physical chemistry approach, evaluating the dustiness of powders can be more difficult. Dustiness can be measured using one of four general methods: 1) mechanical dispersion (vibration); 2) gravity dispersion (drop test); 3) gas dispersion (fluidized bed, for small samples (Boundy, 2006); and 4) resuspension chamber (Hamelmann & Schmidt, 2004).

The biosafety community has often had to conduct risk assessment and risk management in the absence of OELs. For example, no OELs or "infectious doses for organisms" has been established by OSHA even though OSHA expressed some interest in doing so (Johnson, 2003). Currently, biosafety principles are based on assessing hazards of microorganisms according to their infectious capability, virulence and availability of effective treatments and preventative measures; and assigning microorganisms into one of four risk groups according to their hazards and routes of transmission (CDC & NIH, 2007).

Risk Group 1 includes agents not known to cause human disease, such as infectious canine hepatitis virus. Risk Group 2 includes indigenous moderate risk agents associated with human diseases of varying severity, such as salmonella. Risk Group 3 includes indigenous or exotic agents associated with human disease and with a low potential for human-to-human transmission. Risk Group 4 includes dangerous or exotic agents of a life-threatening nature, which may be transmitted via aerosol route and for which there is no available vaccine or therapy, such as hemorrhagic fever viruses. Similarly, binning of engineered nanoscale materials according to their anticipated degree of hazard is under consideration within a "control banding" approach to nanotechnology. In general, control banding means a process in which a single control technology (such as general ventilation or *containment*) is applied to one range or band of exposures to a chemical (such as 1-10 mg/m3) that falls within a given hazard group (such as skin and eye irritants, or *severely irritating and corrosive*). The most developed model for control banding in occupational health has been established by the Health and Safety Executive (HSE) of the United Kingdom (HSE, 2007).

Risk Management

Risk management programs aimed at minimizing the risk of exposure are routinely implemented in the workplace, including research laboratories and health care facilities. Important elements of a risk management program include the establishment of guidelines for installing and evaluating engineering controls such as, exhaust ventilation, education and training of workers in the proper handling of nanomaterials (good work practices), and the development of procedures for selecting and using personal protective equipment (PPE), such as clothing, gloves, and respirators (NIOSH, 2006).

As noted above, the health care and pharmaceutical industries have long recognized the need for controlling occupational exposures to biologically active entities such as pharmaceutical and infectious agents. Biologically active ingredients often are not sufficiently characterized toxicologically to establish health-based OELs. To overcome this deficiency hindering the establishment of rigorous industrial hygiene practices, an alternative approach, based on semi-quantitative criteria for assessing health risks of compounds and effectiveness of control techniques, has been developed and employed by the pharmaceutical industry (Olson et al., 1997; Heidel, 2001).

In this approach known as "exposure banding," substances are assigned into one of five occupational hazard bands using available toxicological information. Each band corresponds to a set of controls necessary to provide protection for workers. The controls can range from open-air handling for low hazard substances to the use of ventilated enclosures and glove boxes for working with high hazards substances. Each band can be further divided into inhalation and dermal (Goede et al., 2003) exposure classes, which are then assigned a set of controls necessary to provide protection for workers.

Similarly, risk from biological hazards is reduced with combinations of laboratory practices and techniques, safety equipment, and laboratory facilities prescribed to four biosafety levels (CDC & NIH, 2007). Biosafety levels correlate, but do not equate with Risk Groups. In deciding which biosafety level is most appropriate for a specific site, the hazard of an agent expressed as an agent's Risk Group and exposure potential related to the mode of transmission, procedural protocols, and experience of staff are assessed. Biosafety Level 1 (BSL-1) represents the most basic level of containment that relies on standard microbiological practices with no special primary or secondary barriers. In BSL-2, the primary hazards to workers come from accidental percutaneous, or mucous membrane exposures, or ingestion of infectious materials. Biosafety cabinets (BSC), splash shields, face protection, gloves, and lab coats are used as primary barriers. In BSL-3 all laboratory manipulations are performed in enclosed equipment, such as biosafety cabinets, and secondary barriers include ventilation requirements to minimize release into the environment. For infectious agents handled under BSL-4, primary hazards come from respiratory, mucous membrane, or broken skin exposures. Complete isolation of workers is achieved with a Class III BSC and/or a full-body, air-supplied positive pressure personnel suit. Secondary barriers include complete isolation with specialized ventilation requirements and waste management systems to prevent the release of viable agents into the environment.

In the case of potential exposures to biological agents, including nanoscale agents outside controlled environments, *NIOSH Interim Recommendations for the Selection and Use of Protective Clothing and Respirators Against Biological Agents* (NIOSH, 2001) suggest using a half-mask, or full facepiece air-purifying respirators with particulate filter efficiencies of P100 for hazards such as hantavirus as a minimum level of protection. Self-contained breathing apparatus (SCBAs) respirators, with a full facepiece operated in positive pressure mode, are recommended for use when hazards and airborne concentrations are either unknown, or expected to be high. Protective clothing, including gloves, lab coats, and booties also provide protection against dermal exposures to biological agents.

NIOSH's *Approaches to Safe Nanotechnology* describes current NIOSH recommendations for control measures to reduce exposures to nanoscale engineered materials in general occupational setting (NIOSH, 2006). In general, control techniques such as source enclosure (isolating the generation source from the worker), and local exhaust ventilation systems are expected to be effective for capturing airborne engineered nanoscale particles based on what is known of nanoscale particle motion and behavior in air (Seinfeld & Pandis, 1998; Hinds, 1999). Current knowledge also indicates that a well-designed exhaust ventilation system with a high-efficiency particulate air (HEPA) filter should effectively remove NPs (Hinds, 1999; NIOSH, 2003). 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 & Liu, 1982; Pui & Kim, 2006). Similarly, it is expected that NIOSH certified respirators can provide the expected levels of protection (NIOSH, 2004).

Conclusion

Current approaches to risk management for engineered nanomaterials, such as engineering control, administrative control, PPE and health surveillance, parallels approaches already in practice in occupational health and biosafety. Further research and investigation is needed to evaluate the effectiveness of these approaches across the spectrum of engineered nanomaterials being used and generated in laboratories and industry.

NIOSH's Nanotechnology Research Center aims to identify the risk implications of nanotechnology for worker health, and to devise ways to protect workers from any identified adverse health effects of working with nanomaterials by developing novel approaches to risk assessment and management. Examples of NIOSH's activities include the following: an inter-disciplinary field team partnering with nano-enabled research and development labs and manufacturing sites to assess exposures and effectiveness of risk management practices; dynamic web-based NIOSH recommendations that are regularly updated to reflect new knowledge obtained through research and surveillance; multiple projects to assess the pulmonary, cardiovascular, dermal and neural effects of engineered NPs; development of risk assessment models and exposure monitoring techniques; and active participation in the development of governmental and non-governmental programs and standards both nationally and internationally. Close collaborations between all nanotechnology stakeholders—academia, government, labor, industry, practitioners and the public—is necessary to ensure that the potential of nanotechnology to improve level of life is realized *at the same time* that occupational health concerns are effectively addressed. With nanotechnology, we still have a chance to do it right the first time.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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