Nanotechnology and Health

ACOEM Nanoparticle Task Force

There has been a considerable scientific, governmental, and public interest in potential adverse health effects associated with exposure to engineered or synthesized nanomaterials. Although such effects have not been reported in humans, there is accumulating evidence from animal studies that exposure to some nanomaterials may be harmful. There is sparse knowledge as to the likelihood, frequency, and intensity of exposures experienced by those working around engineered nanoparticles. Similarly, there is little knowledge regarding the potential existence, type, and dose dependence of adverse health effects, which might result from workplace exposures to engineered nanoparticles. This uncertainty, reflecting a relative lack of research, makes it difficult at present (and probably for the near future) to fully rely upon firm scientific evidence for the development of rational, preventive, and screening measures to protect against such potential effects. Recognizing this predicament, the American College of Occupational and Environmental Medicine (ACOEM) has developed this guidance document for occupational medicine physicians and their colleagues. The purpose of the document is to offer current prudent preventive recommendations on the topics of exposure monitoring, exposure controls, and medical surveillance. This document will not attempt to review the rapidly evolving animal toxicology literature in detail, as any review would be quickly outdated, but general areas of concern will be discussed.

BACKGROUND

Nanomaterials are manufactured in various shapes and sizes. Engineered nanoparticles are defined by most national nanotechnology programs and the International Organization for Standardization as manufactured particles with all three dimensions in the range of 1 to 100 nm. However, some safety and health experts have proposed increasing the upper limit to 450 nm to better encompass the full-size range of particles with potentially similar toxicologic properties. Nanofibers are a form of manufactured nanomaterials with one axis elongated compared with the other two axis dimensions in the nanometer range. Nanofibers include hollow structures (nanotubes) and solid structures (nanorods).[1] Because of their small size, nanoparticles and nanofibers often have different physical and toxicological properties compared with larger particles of the same chemical composition, perhaps in part because of their much greater surface area for any given mass. These size-related properties potentially lead to greater biological reactivity (including an ability to generate reactive oxygen species) and a greater ability to penetrate through membranes and into tissues. Their shape—eg, as a fiber with a high aspect ratio (of the longer to the shorter dimension)—may also impart different toxicological properties. Finally, their physical form (eg, free powder, presence in a slurry or as an agglomerate of particles, or bound in a matrix) will affect the likelihood of biological effect from exposure.

One source of data on the impact of small particle exposure is research on air pollution and ultrafine particles (the size of particles less than 100 nm in diameter, produced unintentionally by combustion and similar processes). These particles have a similar-size distribution to, though different composition than, engineered nanoparticles.[1] Unlike larger particles, such as PM2.5 (the size of fine particles less than or equal to 2.5 μm in diameter) for which mass concentrations are provided in $\mu g/m^3$, ultrafine particles are typically measured in particle number concentrations (no. of particles/cm^3). Epidemiologic studies have evaluated health outcomes in populations environmentally exposed to particulate matter, including fine and ultrafine particles, as a result of air pollution. There is evidence from these studies for increased pulmonary and cardiac morbidity and mortality, such as from asthma and ischemic heart disease, related to increases in ultrafine particulate concentration. The role of ultrafine particle exposures in inducing these effects is a topic of ongoing research. A study in Germany found that reduced lung function, increased respiratory symptoms, and increased need for medications in adult asthmatic patients were significantly associated with exposure to ultrafine particles at mean particle number concentrations from 7700 to 9200/cm^3.[2] Studies of workers exposed to mixtures of fine and ultrafine particulates also have documented declines in pulmonary function and excesses of respiratory symptoms.[1] Experimental human exposure to ultrafine particulate has been associated with alterations in heart rate variability, a potential risk factor for short-term cardiovascular mortality, as well as suggestions of mild inflammatory and prothrombic responses in blood or lavage fluid.[2,3] These findings may predict potential adverse health effects from engineered nanoparticles.

The animal toxicology literature describes a variety of toxicological effects from exposures to specific types of nanoparticles, as well as ultrafine particles, as documented in a recent review article.[4] Animal studies of nanoparticles have, in some cases, documented adverse pulmonary effects, including pulmonary inflammation and fibrosis, and adverse cardiovascular effects, including inflammation, atherosclerosis, and thrombosis. For example, single-wall carbon nanotubes, by pharyngeal aspiration, have caused pulmonary inflammation with granuloma formation and diffuse interstitial fibrosis in mice. There is some animal evidence of tumorigenicity, eg, mesothelioma induction in mice exposed to multiwalled carbon nanotubes by intraperitoneal injection.[1] Some animal studies have demonstrated translocation of nanoparticles from one tissue to a distant site, such as from the nasal cavity to the brain via the olfactory nerve tract.[5] Because the route of administration in these studies is often different from potential workplace exposures and the dose is often larger, one cannot assume that the findings in these studies would apply to humans exposed in occupational settings.

While there is some evidence from animal studies of dermal absorption of certain nanoparticles and ingestion is at least theoretically possible, the most likely route of exposure to nanoparticles in an occupational setting would be by inhalation, as is true for other airborne particles. The site of deposition and potential for absorption after inhalation exposure will be affected by the agglomeration of nanoparticles in air.[1]

Based on the greater toxicity of some compounds in nanoparticle form than in more traditional larger particulate form, there is some evidence that the toxicological effects of nanoparticles may be only partially related to their chemical composition, with some effects instead reflecting the physical properties or shape of the particles.[1] While exposures to nanoparticles in occupational settings are likely to fall below mass-based

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exposure limits, conventional assessment of hazard, based on such limits, may not be relevant to (or protective for) nanoparticles. Thus, gravimetric workplace exposure limits that apply to large particles may not be adequately protective when applied to nanoparticles of the same material.

EXPOSURE CONTROLS

Because of uncertainty regarding the potential for human health effects from exposure to nanoparticles and in light of growing research data indicating adverse health effects in laboratory animals, prevention or reduction of exposure, using the hierarchy of controls, seems prudent. The potential for exposure to nanoparticles, influenced by the quantity used and the form in which the nanoparticles occur, should be considered in designing appropriate controls. Engineering controls, such as source enclosure, local exhaust ventilation, and HEPA filtration, should substantially reduce or completely eliminate exposures. Robust controls that prevent exposures may represent the most prudent response at this time to the lack of information on health effects and dose–response. Employee training in safe work practices is also important. Chapter 8, *Guidelines for Working With Engineered Nanomaterials*, in NIOSH Publication No. 2009-125, provides detailed information regarding exposure controls. As noted in this document, on the basis of available studies, "NIOSH-certified respirators should provide the expected levels of protection if properly selected and fit tested as part of a complete respiratory protection program."[1] The National Institute for Occupational Safety and Health (NIOSH) also indicates that it is prudent to consider the use of protective clothing and gloves to minimize dermal exposure, although there are no scientific data from which to select the most effective protective equipment.

EXPOSURE ASSESSMENT

The optimal methods for exposure assessment of engineered nanoparticles will likely be different from those used in traditional industrial hygiene monitoring for large particles. It is not yet clear what metric of exposure best correlates with the risk of adverse health effects from nanoparticles. Therefore, it is difficult to make recommendations for exposure assessment methodology. Nanoparticles, like ultrafine particles, have very low mass relative to larger particles. Measurements of mass concentration ($\mu g/m^3$) are likely to be low, despite high particle number concentrations. There is some rationale in the air pollution literature for measuring particle number concentrations, as is sometimes done for ultrafine particles. Other approaches might involve size fractionation of airborne particulate or particulate surface area measurement or estimation. Some of these methods are not routinely available. In the absence of comprehensive toxicology data on and exposure limits for nanomaterials, some authors have advocated a control banding approach to estimate the potential for exposure to and for hazards from nanoparticles, thus providing a rational basis for control recommendations.[6] As described by the authors and further detailed in this publication, control banding is an instrument that "uses categories, or 'bands,' of health hazards, which are combined with exposure potentials, or exposure scenarios, to determine desired levels of control."

One factor to consider is that there is a significant background level of nanoparticles in the environment. Physicians and EHS professionals should consider this information during exposure assessment efforts, as well as in conducting risk assessments and risk communication.

Regarding exposure assessment, NIOSH recommends that "Regardless of the metric and method selected for exposure monitoring, it is critical that measurements be taken before production or processing of a nanomaterial to obtain background nanoparticle exposure data."[1] The ultimate utility of such baseline measurements will depend, of course, on the selection of a proper method that provides meaningful data for follow-up exposure and risk assessments. More information about recommended approaches is available in Chapter 7 on *Exposure Assessment and Characterization* in NIOSH Publication No. 2009-125.[1]

NIOSH currently recommends a program of hazard surveillance in workplaces in which nanoparticles are handled. Such surveillance includes identifying the nature of nanoparticles used, types of exposure assessment, measures to control exposures (including assessment of their efficacy), characterizing the potentially exposed workers by job title, tasks, and area, and documenting this information, including changes over time.

MEDICAL SURVEILLANCE

The current NIOSH recommendation regarding medical surveillance for workers potentially exposed to nanoparticles states:

> Currently there is insufficient scientific and medical evidence to recommend the specific medical screening of workers potentially exposed to engineered nanoparticles. Nonetheless, this lack of evidence does not preclude specific medical screening by employers interested in taking precautions beyond existing industrial hygiene measures. If nanoparticles are composed of a chemical or bulk material for which medical screening recommendations exist, these same screening recommendations would be applicable for workers exposed to engineered nanoparticles as well.[7]

ACOEM endorses this recommendation, because the human health effects, if any, from workplace nanoparticle exposure are unknown, meaning that appropriately targeted and specific medical surveillance programs cannot be defined at this time. Furthermore, it is uncertain whether screening methods commonly used in medical surveillance, such as spirometry, will have the sensitivity and specificity to detect potential early adverse effects from exposure to nanoparticles. There are more sensitive tests for pulmonary injury and inflammation that have been used in other settings and might have applicability for workers exposed to nanoparticles such as cytokine measurements. However, their utility, sensitivity, and specificity have not been evaluated for this setting. NIOSH recognizes that there are potential adverse impacts from the implementation of medical testing protocols with undefined positive predictive value, including anxiety in those with positive results and the cost of required follow-up evaluation of abnormal results. In spite of these difficulties and uncertainties, two NIOSH scientists have recently recommended that a basic medical surveillance program be considered for groups of workers exposed to nanoparticles for which toxicology data suggest that there might be a risk of disease in exposed individuals. They provide the example of workers exposed to carbon nanotubes for which animal toxicology data suggest, at some dose, a risk of malignant and nonmalignant respiratory disease.[8]

For nanoparticles composed of materials for which there are already medical surveillance recommendations, NIOSH suggests that this screening would be applicable for those working around the nanoparticles. Because of the low mass of nanoparticles, it is unlikely that exposures would exceed the action levels for medical surveillance, typically in $\mu g/m^3$, assigned for the parent material. Determining appropriate thresholds for performing medical surveillance based on other features of the exposure, such as particle number concentration, may be problematic, given limited knowledge about dose–response.

NIOSH suggests considering the use of exposure registries to identify workers exposed to nanoparticles, which would permit longitudinal follow-up and, if appropriate, examination of these cohorts for the presence of findings or diseases that may be associated with their exposures. In addition to facilitating voluntary epidemiologic research, the maintenance of exposure registries at the present time may aid the implementation of risk communication and

targeted medical surveillance necessary in the future as a potential recommendation stemming from research findings. The sharing of de-identified exposure data within industrial sectors may augment the establishment of industrial hygiene benchmarks and may facilitate product stewardship efforts.

RECOMMENDATIONS FOR FURTHER RESEARCH AND ACTION

On the basis of epidemiologic studies related to particulates, particularly ultrafine particles, and animal toxicology studies, it is certainly plausible that exposures to nanoparticles in sufficient concentration in occupational settings can result in pulmonary inflammation and its consequences. The potential for adverse cardiovascular morbidity and mortality is also of concern. As additional studies become available, it may be possible to define other plausible outcomes. At this time, it is not clear that such effects have ever occurred in workers handling nanoparticles. As dose–response relationships become better defined, it may be possible to determine the likelihood of adverse effects in occupational populations.

Currently, there are insufficient data to permit the conduct of risk assessments for individual types of nanomaterials, with limitations affecting each step of the risk assessment process—hazard identification, hazard characterization, exposure assessment, and risk characterization. Needed information is lacking regarding the appropriate exposure metric, regarding exposure data from workplace settings, and regarding toxicity data, including dose–response information and information regarding absorption, distribution, metabolism, and excretion. There is also a need for techniques and equipment to permit practical and appropriate exposure monitoring in workplaces. Savolainen et al discuss in detail the needed information for and current difficulties with risk assessment of nanomaterials.[9] ACOEM supports the conduct of appropriate screening in vitro testing and animal toxicology research that utilizes routes of exposure and doses that would permit extrapolation to occupational exposure settings and performance of dose–response assessments and ultimately risk assessments. Of course, the variety of types of nanoparticles of different composition, size, and form would require the conduct of multiple studies to fill current knowledge gaps. There should be partnership and dialogue between ACOEM and agencies, such as NIOSH and the 27-agency collaboration sponsored by the National Nanotechnology Initiative,[10] to focus the research in areas relevant to workplace risk assessments. ACOEM also supports research as to the best methods of exposure assessment, which is also required for risk assessments.

Robust exposure controls, while desirable from a preventive standpoint, will, most likely, prevent any health effects that might be found through epidemiologic or clinical assessments of groups of workers handling nanomaterials. However, if exposure assessment does document exposures in a range where health effects might occur (based on animal or other studies) or if symptoms occur in a population of workers, ACOEM supports the conduct of appropriate targeted medical screening. If significant exposures or symptoms were to occur, it would be appropriate to collaborate with NIOSH in evaluating them, including sharing of group findings from medical screening. Biological monitoring could be a useful approach to documenting exposure and assessing internal dose for those materials, such as metals, where reliable testing and interpretive guidance are available.

It is important to note that workplace exposure to engineered nanomaterials might not be confined to the initial manufacturing processes but might also occur during maintenance or modification activities, such as cutting, sanding, or drilling, which disrupt finished products or components fabricated with nanomaterials. At the present time, material safety data sheets and other safety information that accompanies finished products may not reliably indicate the presence of engineered nanomaterials. ACOEM supports the proper labeling of products containing nanomaterials, especially if anticipated use, maintenance, or handling might result in potential nanoparticle exposure.

ACOEM supports the use of voluntary exposure registries by companies or consortia of companies, particularly when there is an indication that controls are not able to prevent all exposure. The diversity of types (composition/chemical structure, size, form) of nanoparticles will make establishment of exposure registries of like-exposed individuals difficult. Issues such as accurately defining exposures, noting evolution in exposures over time, and ensuring comparability of groups of workers to be considered together may limit the feasibility and utility of this approach. On the contrary, historical experience with other occupational hazards, such as asbestos and benzene, has found that even relatively crude exposure classifications may be of epidemiologic value. When indicated, ACOEM and individual organizations should collaborate with NIOSH in the development of these registries, including selection of the types of data to be collected for future use. Trout and Schulte[8] from NIOSH, in a recent publication, provide a detailed discussion of relevant considerations for the initiation of exposure registries and epidemiologic studies of workers exposed to nanomaterials.

ACOEM will continue to support educational programs, to be presented at venues such as AOHC and component meetings, on the toxicology, epidemiology, and risk assessment of nanoparticles, as well as prudent preventive measures for workers exposed to nanoparticles.

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