# Nanotechnology and Health

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Potential adverse health effects associated with exposure to engineered or synthesized nanomaterials have not been reported in humans; however, there is accumulating evidence from animal studies that exposure to some nanomaterials is harmful. While there is uncertainty as to the likelihood, frequency, and intensity of exposures experienced by those working around engineered nanoparticles, the American College of Occupational and Environmental Medicine has developed this guidance document for occupational medicine physicians and their colleagues to offer prudent preventive recommendations on the topics of exposure monitoring, exposure controls, and medical surveillance.

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 is 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 and 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will not attempt to review the rapidly evolving animal toxicology literature in detail, as any review would be quickly outdated, but general areas of concern will be discussed.

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## 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. 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 due to 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—for example, 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 exposure and potential biological effects.

One source of data on the impact of small particle exposure is research on air pollution and ultrafine particles (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 $PM_{2.5}$ (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 often measured in particle number concentrations (number of particles/$cm^3$). Epidemiological 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 asthmatics 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 prothrombotic 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] Animals 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

(SWCNT), administered by pharyngeal aspiration, have caused pulmonary inflammation with granuloma formation and diffuse interstitial fibrosis in mice. There is some animal evidence of tumorigenicity, for example, mesothelioma induction in mice exposed to multi-walled carbon nanotubes (MWCNT) by intraperitoneal injection.[1] One study found that inhalation of MWCNT at a concentration of 5 mg/m$^3$ for 15 days promoted the development of bronchiolo-alveolar adenomas and lung adenocarcinomas in mice previously exposed to the initiator, methylcholanthrene.[5]

Based on these and other findings, in 2014 the International Agency for Research on Cancer (IARC) assigned certain MWCNT (MWCNT-7) to Group 2B (possibly carcinogenic to humans, based upon sufficient evidence in experimental animals) and the rest of MWCNT to Group 3 (not classifiable as to their carcinogenicity to humans). SWCNT were also classified as Group 3.[6,7] 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.[8] 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.

There is a single case report of a worker who developed nickel sensitization with new onset of reactions to nickel earrings and a belt buckle and with a positive patch test after uncontrolled exposure to a nickel nanoparticle powder. The worker also reported symptoms suggestive of allergic rhinitis temporally associated with exposure and had a significant increase in $FEV_1$ after inhalation of a bronchodilator.[9]

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. Nanoparticles are of respirable size, such that they can reach the alveolar region of the respiratory tract.[10] The site of deposition and potential for absorption after inhalation exposure will be affected by the agglomeration of nanoparticles in air.[1] Based upon 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 exposure limits, conventional assessment of hazard, based upon 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 high-efficiency particulate air (HEPA) filtration, should substantially reduce or completely eliminate exposures.[11] 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. Regarding respirators, the National Institute for Occupational Safety and Health (NIOSH) recommends their use when adequate engineering controls to prevent exposure are not feasible. NIOSH states: ''Current respirator performance research suggests that NIOSH's traditional respirator selection tools apply to nanoparticles. NIOSH-certified respirators should provide the expected levels of protection, consistent with their assigned protection factor, and should be selected according to the NIOSH Respirator Selection Logic...''[9] NIOSH also indicates that it is prudent to consider the use of protective clothing and gloves to minimize dermal exposure, although there is limited information available from which to select the most effective protective equipment.

## EXPOSURE ASSESSMENT

The optimal methods for exposure assessment of engineered nanoparticles may be different than 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 challenging to make recommendations for optimal 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. Despite this concern, the recommended exposure limits that NIOSH has issued are mass-based. 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. A number of tiered approaches to exposure assessment for nanomaterials, which consist of information gathering, basic assessment, and comprehensive assessment tiers, have been proposed. NIOSH's Nanomaterial Exposure Assessment Technique (NEAT 2.0) is an example of such a tiered approach, which aims to assess time-weighted average (TWA) exposures by collecting personal-breathing-zone filter-based samples during a worker's activity over the entire workday.[12] 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.[13] 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 ultrafine particles in the environment. Physicians and environmental health and safety 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, upon 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.

## OCCUPATIONAL EXPOSURE LIMITS

NIOSH has to date established recommended exposure limits (RELs) for two categories of nanomaterials. An REL for carbon nanotubes and nanofibers is based upon quantitative risk assessment from available short-term and sub-chronic animal studies. The endpoints of concern in the animal studies are pulmonary inflammation, granulomas, and pulmonary fibrosis. Working lifetime exposures to 0.2 to 2 $\mu g/m^3$ (8-hour time-weighted average [TWA] concentration) were estimated to be associated with a 10% excess risk of early stage lung effects (minimal granulomatous inflammation or alveolar septal thickening, grade 1 or higher). Based upon this, the REL for carbon nanotubes and nanofibers is 1 $\mu g/m^3$ of respirable elemental carbon as an 8-hour TWA concentration.[14] NIOSH has also established an REL for ultrafine titanium dioxide (including engineered titanium dioxide nanoparticles) of 0.3 $mg/m^3$ as a 10-hour TWA concentration.[15] The most relevant data for assessing the health risk to workers are results from a chronic animal inhalation study with ultrafine (less than 100 nm) $TiO_2$ in which a statistically significant increase in adenocarcinomas was observed. This recommendation represents levels that over a working lifetime are estimated to reduce risks of lung cancer to below 1 in 1000.

## MEDICAL SURVEILLANCE

The previous NIOSH recommendation regarding medical surveillance for workers potentially exposed to nanoparticles stated[16]:

> ''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.''

ACOEM endorses this recommendation for most nanomaterials, 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. Further, 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. Nevertheless, more recently, NIOSH has recommended medical surveillance for workers exposed to carbon nanotubes and nanofibers above the REL of 1 $\mu g/m^3$ based upon their recognized pulmonary toxicity, including pulmonary fibrosis, in animals with the intent of detecting potential early adverse health effects. Initial evaluation should include an occupational and medical history, focusing specifically on respiratory symptoms, a physical examination focused on the respiratory system, spirometry, and a baseline chest x-ray. Periodic evaluations should include an occupational and medical history and spirometry at intervals not greater than every 3 years. In addition, NIOSH recommends periodic aggregate data analysis of groups of workers.[11]

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 upon 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 epidemiological 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. Even in the absence of formal medical surveillance protocols, exposure registries may ultimately be useful in tracking the health status of various members of a nanomaterial workforce.[17]

## RECOMMENDATIONS FOR FURTHER RESEARCH AND ACTION

Based upon 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 could 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, there is no evidence 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.

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,[18] to focus the research in areas relevant to workplace risk assessments. ACOEM also supports research as to the best methods of exposure assessment, which are 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 epidemiological 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 upon animal or other studies) or if symptoms occur in a population of workers, ACOEM supports the conduct of appropriate targeted medical surveillance. 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 surveillance. 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 is 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, safety data sheets and other safety information that accompanies finished products may not reliably indicate the presence of engineered nanomaterials or their potential release during typical or atypical activities that may disturb or disrupt the product. ACOEM supports the proper labeling of products containing nanomaterials, especially if reasonably anticipated use, maintenance, or handling might result in potential nanoparticle exposure. For a distributor or seller of a finished product or part, that will require careful tracking of nanomaterial content in all precursor materials and components.

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 other hand, historical experience with other occupational hazards, such as asbestos and benzene, has found that even relatively crude exposure classifications may be of epidemiological 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, provide a detailed discussion of relevant considerations for the initiation of exposure registries and epidemiologic studies of workers exposed to nanomaterials.[19]

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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