Nanotechnologies and Nanomaterials in the Occupational Setting

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Workers are generally the first people in society to be exposed to the hazards of an emerging technology and nanotechnology is no exception. The workplaces where nanomaterials are developed, investigated, manufactured, used, and disposed of are quite varied and they span all economic sectors. To protect the health and safety of workers in all of these workplaces requires a concerted effort that includes: hazard identification, exposure assessment, risk characterization, and risk management. In this paper, the current status of efforts in each of these categories will be discussed. Although there are more than 1,000 “nano-enabled” products in commerce, there is virtually no human evidence of adverse health effects attributed directly to engineered nanoparticles, in part, due to the current observations that exposures are limited and short. Nonetheless, there is a coalescing body of evidence from animal and in vitro studies that indicates that various types of nanomaterials may be hazardous to workers. However, there are also limited published data on exposure and practically no comprehensive and quantitative exposure assessments. There have been few formal risk assessments published and no occupational exposure limits (OELs) specifically for engineered nanoparticles have been officially promulgated, although several exposure guidelines have been published by nanomaterial producing companies. A precautionary approach to risk management has been strongly advocated by various health authorities internationally and there is an array of useful general risk management guidance, but guidance for many specific operations, engineering controls, and medical surveillance is lacking. The next major phase, in addition to further hazard and control research, in the efforts to protect workers as nanomaterials become more widely available in commerce is to focus on assessing barriers that prevent implementation of precautionary guidance and to identify and evaluate worker populations.

Key words: nanotechnologies, nanomaterials, occupational exposure

Introduction

The occupational settings where exposure to nanomaterials can occur range across many sectors and involve a broad array of scientific disciplines and industrial operations. This is, in part, due to the fact that nanotechnology is not an industry, but an enabling technology that contributes to the value chain (the activities and companies that give products additional value). A useful way to think about the occupational settings involving nanotechnology is to take a life cycle view of workplaces as shown in Figure 1. Occupational exposures can occur all along the life cycle of a nanomaterial from research through scale-up, manufacturing, product development, and end of life. This life-cycle description of workplaces can then be seen to occur across many sectors and for many types of nanomaterials. The combination of (workplaces) x (sectors) x (nanomaterial types) yields a three-dimensional matrix of workplaces each with different potential for occupational exposure by function, tasks, or activity [Schulte et al., 2009]. The picture is further complicated by the fact that the universe of potential engineered nanomaterials is extremely large due to an array of different physicochemical parameters, impurities, and manufacturing conditions. The diversity of occupational settings also impacts the development of guidance on controls and the conduct of medical surveillance and epidemiologic research. Consequently, at this time, there are many uncertainties about the hazard of the nanomaterials, and the potential or actual exposure and resulting risks to workers. In this paper, we

Figure 1: Matrix of occupational settings where exposure to engineered nanomaterials could occur
Evidence of hazard of nanomaterials

There is a small but growing literature on the biological effects of various engineered nanomaterials. These include in vitro and in vivo studies with a large proportion focused on carbonaceous nanoparticles (carbon nanotubes, fullerenes and carbon black), nano-metals, and metal oxides particularly, titanium dioxide, as well as including studies of quantum dots and various other types of nanoparticles. The most informative studies for assessing worker inhalation hazards are animal inhalation studies. However, for the most part, they have been initial studies of short duration (< 90 days). Using short-term studies to evaluate the hazard potential of industrial materials has been the historical approach taken to identify high priority candidates for longer-term studies. Although there is an absence of long-term animal studies of specific engineered nanomaterials, chronic inhalation studies in animals have been performed for some nano-structured (also known as “ultrafine”) particles [Mauherly et al., 1987; Heinrich et al., 1995; Nikula et al., 1995]. These studies have shown that these ultrafine poorly-soluble particles are lung carcinogens in the rat at lower mass doses than for larger (fine-sized) particles [Martin et al., 1977; Lee et al., 1985; Muhle et al., 1991]. These poorly-soluble nanoparticles also cause greater pulmonary inflammation in rodent lungs than larger-sized particles of the same chemical composition [Bermudez et al. 2002; Elder et al. 2005; Bermudez et al., 2004]. This persistent inflammation is related to the total particle surface area dose (which is greater for smaller particles of an equal mass dose), and the associated generation of reactive oxygen species, cell damage, and cell proliferation appear to be the indirect mechanisms involved in the carcinogenesis [Baan, 2007; Schins and Knaapen, 2007]. While it is beyond the scope of this paper to review the studies for each type of nanoparticle, a few general lessons can be drawn. First, various characteristics of a nanoparticle such as size, shape, chemistry, oxidant generating capacity, surface functionalization, and rate of dissolution appear to determine toxic potentials [Sayes et al., 2004; Warheit et al., 2005; Bergamaschi et al., 2006; Ding et al., 2009]. Although nanosized materials appear more toxic on an equal mass basis than larger particles of the same composition, there is limited evidence that nanosize confers unique toxicity on materials, since nano and fine-sized particles exhibit similar potency when dose is normalized to equal surface area of particles administered [Drew, 2009]. However, some studies have shown the potential for unique toxicity of some nanomaterials due to their small size and ability to interact with cell machinery. For example, single-wall carbon nanotubes can interfere with mitosis (cell division) resulting in genotoxicity and abnormal chromosome number [Sargent et al., 2009]. Individual titanium dioxide nanoparticles have been observed inside cell organelles including the cell nucleus [Geiser et al., 2003]; and nanoparticles depositing in the nasal region can enter the brain via neuronal transport in the rat [Oberdörster et al., 2002]. Second, short-term exposures of rodents to single and multi-wall carbon nanotubes have resulted in persistent pulmonary fibrosis [Shvedova et al., 2009]. In addition, evidence is accumulating that some types of carbon nanotubes (multi-wall) can act like fibers and penetrate the pleura and may follow the fiber carcinogenesis paradigm [Poland et al., 2008; Porter et al., 2010; Mercer et al., 2010]. Third, long-term (2 year) inhalation exposure of rats to titanium dioxide has resulted in lung tumors, with the tumors noted at substan-}

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Nature of the risk
The limited hazard and exposure data on various nanomaterials also limits the extent to which risks can be assessed. Only a few risk assessments have been put in the public domain (e.g., for public comment or by reference) but practically none have been published. In 2005, the National Institute for Occupational Safety and Health (NIOSH) presented for public comment a risk assessment on titanium dioxide that used dose-response data from chronic inhalation studies in rats [Lee et al., 1985; Mauderly, 1987; Muhle et al., 1991; Heinrich et al., 1995]. The risk assessment method involved estimating particle surface area dose in lungs associated with a specified excess risk (e.g., 1/1000) of lung tumors in rats and extrapolating that dose to humans by adjusting for species differences in the factors influencing lung dose (e.g., particle deposition fractures, lung surface area, and breathing rates) [NIOSH, 2005]. The risk assessment was conducted using surface area metrics to fit the dose-response data for both fine and ultrafine titanium dioxide then converted to mass concentration (using specific surface area (m²/g) of each particle size) since workplace exposure measurement methods typically use mass concentration. The estimated lower 95% confidence limit for a 1/1000 excess risk of lung tumors in rats and extrapolating that dose to lungs associated with a specified excess risk (e.g., 1/1000) was 0.021 mg·m⁻³, compared to approximately 1 mg·m⁻³ for the fine-sized titanium dioxide. Both are lower than the current occupational exposure limits (OELs) that do not take into account particle size.
A similar approach was taken with carbon nanotubes using data from Ma-Hock et al., (2009). The risk assessment estimated risks of pulmonary inflammation and fibrosis over a working lifetime at low mass concentration (8-hr time weighted average), including at the limit of quantitation (7 µg·m⁻³) of the NIOSH analytical method for elemental carbon [NIOSH, 1994]. Carbon nanotubes are a form of pure elemental carbon. The NIOSH method was developed and validated as a method to assess exposure to diesel particulate by measuring for elemental carbon, but is not specific for any particular form of elemental carbon. Since there appears to be significant residual risk at the limit of quantitation for elemental carbon and since carbon nanotubes are fiber shaped, ultimately a fiber count type approach is likely to be needed.
An interim OEL for multi-walled carbon nanotubes was proposed by the Japanese New Energy and Industrial Technology Development Organization [Kobayashi et al., 2009]. This interim OEL was 0.21 mg·m⁻³ (although based on information provided, it would be 0.021 mg·m⁻³ after accounting for the 10 m³ air breathed per day in workers). Producers of two types of multi-walled carbon nanotubes (MWCNTs) have proposed OELs based on subchronic inhalation studies in rats [Ma-Hock et al., 2009; Pauluhn, 2010a]. Pauluhn (2010b) started with the no observed adverse effect level (NOAEL) of 0.1 mg·m⁻³ and applied various interspecies extrapolation factors resulting in an overall factor of 2 and proposed an OEL of 0.05 mg·m⁻³ for MWCNT (Baytubes) [Pauluhn, 2010a]. Nanocyl (2009) applied an overall assessment factor of 40 to the lowest observed adverse effect level (LOAEL) of 0.1 mg·m⁻³ to estimate an OEL of 2.5 µg·mg·m⁻³ for 8-hr/day exposure [Ma-Hock et al., 2009]. From a workshop in 2009 on risk assessment held by the OECD, the general consensus emerged "...that the traditional risk assessment paradigm for chemicals will continue to guide approaches to the risk assessment of nanomaterials [OECD, 2010]. However, because of the limited amount of empirical data on nanomaterials, many of the assumptions and estimations employed in chemical risk assessments need to be evaluated for nanomaterials." Critical in this regard is the need to consider metrics that include surface area and particle counts even though it is expected that risk assessment results will continue to be reported in terms of mass based methods. However, the limitations of mass-based approaches (e.g., LOD of measurement methods) should be addressed in the future, as more toxicological data are generated to identify the most biologically-relevant dose metric and as more practical field instrumentation is available, different metrics from mass may be used. Although current risk assessment efforts are using the available dose-response data from animal studies, future risk assessments may utilize data from epidemiological research. However, for workforces involved with nanomaterials, this will be a difficult task due to the diversity of workplaces, types of nanomaterials, relative relevancy of exposures, and various other issues [Schulte et al., 2009]. This is not to say that epidemiologic studies of nanomaterial workers should not be conducted. On the contrary, such studies are very important in assessing actual risks. Already various exploratory studies are underway and studies involving biomarkers of exposure or response may be a good first step [Schubauer-Berigan and Dahm, 2010].

Issues in management of the hazards and risks

a) Utility of control technologies
The general guidance provided by NIOSH and other government agencies is that properly used engineering controls, good work practices, and personal protective equipment (e.g., N95 respirator) can be effective in reducing or preventing exposure to engineered nanoparticles when properly instituted within a risk management program [NIOSH, 2009a]. This guidance is based on assessment of the effectiveness of controls used to control biologically active dusts in the pharmaceutical industry and other fine powders in various industries. Limited field and laboratory investigations have validated this guidance specifically for engineered nanomaterials [Methner et al., 2010; Shaffer and Rengasamy, 2009; Lee et al., 2010].
Control banding is a qualitative strategy for assessing and managing hazards associated with chemical exposures in the workplace and may be applied to engineered nanoparticles. The concept is used to manage exposures to potentially toxic material through the application of one of four recommended control approaches. This concept is based on the premise that although there are many chemicals with varying toxicity, there are a limited number of controls available. To determine the appropriate control strategy, one must consider the potential toxicological characteristics of a particular chemical substance and the potential for exposure. As the potential for harm to the worker increases, the greater degree of control is needed to manage the risk [NIOSH, 2009b].
The four control bands are usually:
Band 1: Use good industrial hygiene practice and general ventilation
Band 2: Use engineering control, typically local exhaust ventilation
Band 3: Enclose the process
Band 4: Seek expert advice
Another tool, CB Nanotool, bases the control band for a particular task on the overall risk level (RL) which is determined by a "severity" score and a "probability" score. The severity score is determined by the sum of points assigned to the following:

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factors: surface chemistry, particle shape, particle diameter, solubility, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity, and hazard potential of the nanomaterial and the macro-parent material. The overall probability score is based on the following elements: estimated amount of nanomaterial used during the task, dustiness or mistiness, number of employees with similar exposures, frequency of operation, and duration of operation [Paik et al., 2009]. This numerically scored exposure banding still leads to the four Control Bands.

One limitation to control banding of nanomaterials is that there is very little toxicological data on which to both recommend control levels other than the highest two levels and evaluate the validity of the tool. As health hazard studies continue to expand, and the understanding of the toxicity of nanomaterials improves, the severity parameter scores may be adjusted to reflect the new knowledge and thereby affect the severity score to elicit a more defined control band [Zalk et al., 2009]. Unlike the use of control banding for chemical exposures, there are very few comprehensive tools developed for its use with nanomaterial exposures. One useful source, however, is the GoodNanoGuide (www.goodnanoguide.org), an internet based platform for the exchange of ideas on handling nanomaterials.

b) Establishment of OELs
Practically no OELs have been officially promulgated for engineered nanomaterials; however, some candidate or recommended OELs are in the public domain. These have been summarized in a recent paper which identified 16 proposed OELs for nanomaterials [Schulte et al., 2010]. Since there is great variability among engineered nanomaterials, some believe that toxicity is particle specific and that generalizations cannot be made [Warheit et al., 2005]. However, it may be that size will be the ultimate predictor or most weighted characteristic. This still requires investigation. In the meantime, given the large number of specific nanomaterials, it may be that the OELs should be developed on a categorical basis [Maynard and Aitken, 2007].

c) Prevention through Design (PtD)
PtD is an approach (and in the U.S., a national initiative) to design out hazards rather than address them when there are exposures. PtD is particularly applicable to nanomaterials at the molecular and process scales. At the molecular scale, there is potential for modification of molecules to retain commercial and scientific functionality while reducing toxicity [Sayes et al., 2004; Sayes et al., 2006; Lewinski et al., 2008]. At the process scale, companies can look to the pharmaceutical industry for engineering controls that could be adopted for potentially hazardous nanomaterials. Hazard banding and control banding also has its origins in the pharmaceutical industry.

d) Establishment of exposure registries
Exposure registries manage enrollment lists of persons likely to have been exposed to occupational hazards and can serve as a basis for conducting epidemiologic research, risk communication, and medical surveillance [Schulte and Kaye, 1988]. Exposure registries have been used in public health for over 50 years and may have value with the widely dispersed workforce that is illustrated by the large number of different workplaces noted in Figure 1 [Trout and Schulte, 2010].

e) Conduct of medical surveillance
Medical surveillance is a means of assessing the effectiveness of control and prevention approaches for workers such as substitution, use of engineering and administrative controls, and personal protective equipment (PPE). It is a means to identify any failures of primary prevention strategies and to identify in asymptomatic workers biologic changes early in the natural history of disease to make therapy more efficient.

For workers involved with nanomaterials, uncertainty about the hazards led NIOSH (2009c) to conclude that “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.” NIOSH also recommended hazard surveillance and use of prudent measures to control exposure to engineered nanoparticles. With the increase in knowledge about adverse pulmonary effects including pulmonary fibrosis from carbon nanotubes, NIOSH in 2010, is considering more specific medical screening including baseline pulmonary function testing, chest x-ray, and measurement of markers of fibrosis for workers in operations involving exposure to carbon nanotubes and fibers.

Next phase of effort
In the future, two areas of emphasis beyond those described in this paper, merit additional attention. One is the need to assess the extent to which there is compliance with the precautionary guidance including the use of effective controls that has been provided by various health authorities. The other is the need for heightened efforts to identify groups and cohorts of nanomaterial workers who could be enrolled in exposures registries or included in epidemiological studies. Related to epidemiologic research is the need to identify biomarkers of exposure or effect that might be useful in studies of workers [Schulte et al., 2009].

Conclusion
It is relatively early in the commercialization of nanomaterials. The workforce involved with them and the workplaces where exposures might occur has not been well characterized. This is an important objective. Meanwhile, there is need to continue toxicologic research with further emphasis on long-term inhalation studies of chronic effects. There is need for a broader effort to assess the extent and magnitude of exposure to specific engineered nanoparticles and to do this using an array of metrics. Although there are many uncertainties about hazards, exposures, and risks from nanomaterials, there is sufficient evidence to continue to warrant taking a precautionary approach to controlling exposures and considering the potential risks to workers [Schulte and Salamanca-Buentello, 2007]. Hazard and exposure information should be combined in risk assessments that will allow for developing interim OELs. Exposure registries and epidemiologic research should be considered and exploratory efforts in these areas continued. By adopting such a multifaceted precautionary approach, the health and safety of workers can be protected as this worthwhile technology develops.

References

KEYNOTES
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