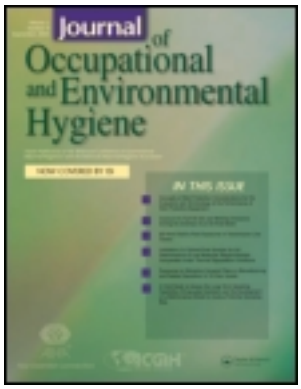

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A Strategy for Assessing Workplace Exposures to Nanomaterials

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This article describes a highly tailorable exposure assessment strategy for nanomaterials that enables effective and efficient exposure management (i.e., a strategy that can identify jobs or tasks that have clearly unacceptable exposures), while simultaneously requiring only a modest level of resources to conduct. The strategy is based on strategy general framework from AIHA® that is adapted for nanomaterials and seeks to ensure that the risks to workers handling nanomaterials are being managed properly. The strategy relies on a general framework as the basic foundation while building and elaborating on elements essential to an effective and efficient strategy to arrive at decisions based on collecting and interpreting available information. This article provides useful guidance on conducting workplace characterization; understanding exposure potential to nanomaterials; accounting methods for background aerosols; constructing SEGs; and selecting appropriate instrumentation for monitoring, providing appropriate choice of exposure limits, and describing criteria by which exposure management decisions should be made. The article is intended to be a practical guide for industrial hygienists for managing engineered nanomaterial risks in their workplaces.

Keywords exposure assessment strategy, exposure management, nanomaterials

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INTRODUCTION

Scope of Exposed Population of Workers

Nanotechnology encompasses a collection of technologies and approaches that involve manipulating matter at the scale of approximately 1–100 nanometers (nm). Within this size range, purposely engineered structures, devices, and systems can have novel functions and properties that are associated with their scale.[1] Nanotechnology grows out of a number of scientific fields, including chemistry, biology, physics, optics,

and mechanics and has been hailed by some as the next industrial revolution. In recent years, nanotechnology has grown rapidly across a range of industries, including pharmaceuticals, materials, medicine, agriculture, electronics, national defense, fiber optics, and energy.[2] Based on the promise of the technology to lead to new jobs and economic growth, there has been significant investment in this technology by governments and industry worldwide.[3,4]

An estimated 2 million new workers will be exposed to engineered nanomaterials in occupational environments over the next 15 years.[5] Consumer products that contain nanomaterials are also becoming more commonplace, and it is only a matter of time before a significant proportion of the population will use or come into contact with products containing nanomaterials.[6] However, the earliest and potentially the most significant exposures and risks will likely be in the occupational arena. There are several industry sectors and processes where worker exposures to nanomaterials have the potential to be significant if not properly contained, including chemical and pharmaceutical companies, construction and manufacturing (e.g., powder handling and cement), electronics, and communications. In addition, potential exposure to engineered nanomaterials can be broad. At an industrial scale, nanomaterials can be produced and used in high volumes with relatively uniform composition and characteristics in a given occupational environment. However, in research and development activities in universities and nanotech start-up companies,[7] lower volumes of materials with more diverse compositions and characteristics are likely to be used. In both settings, traditional ultrafine sources such as welding, diesel exhaust, and other combustion processes may also be present.

Potential Occupational Health Implications

Despite the large investments in nanotechnology, corresponding investments in environmental, health, and safety aspects of this technology and its processes and products have not been as high.[8] Much is still relatively unknown regarding the health risks of nanomaterials. Additionally, key mechanisms for exposure and toxicity effects of manufactured and incidental nanomaterials on humans remain poorly understood, including (a) how long do manufactured nanomaterials persist in the atmosphere; (b) how stable are nanomaterials over time, given specific occupational conditions; (c) what is the effect of particle shape on their fate and transport; (d) what are likely routes of exposure (e.g., inhalation, dermal, ingestion, and ocular); (e) what are the metrics by which exposure should be measured (e.g., particle mass, number, or surface area [SA] concentration); (f) what are key mechanisms of translocation to different parts of the body; and (g) what are possible mechanisms of toxicity, including oxidative stress due to surface reactivity, presence of transition metals leading to intracellular calcium and gene activation, and intracellular transport of nanomaterials to the mitochondria.[9] In assessing overall risk, both exposure and hazard are poorly understood.

In this article, we have focused attention on inhalation exposures. Besides inhalation, the other exposure mechanism is via the dermal route. Because the published data on dermal exposure to nanomaterials are sparse and inconsistent, we have decided not to address dermal exposure here. It remains an area for future research.

Exposure, broadly speaking, is defined as the intensity (i.e., concentration) of the contaminant at an appropriate interface between the environment and the individual over a time interval that has biological relevance (e.g., an adverse health outcome). Uncertainty exists regarding the appropriate metric by which intensity should be measured for inhalation and dermal exposures.[10,11] Traditionally, mass concentration has been regarded as the most appropriate exposure metric associated with health effects of particle exposures. However, the appropriateness of the mass concentration metric for ultrafine particles remains questionable,[12] as particle number and SA concentrations have been proposed as more suitable alternatives for nanomaterials. This distinction has important implications for exposure assessment to engineered nanomaterials that will be described in the following sections.

Uncertainty around chronic and acute exposure also remains. Related to the uncertainty in the overall exposure metric is lack of availability of suitable instruments. For most nanomaterials currently in use, occupational exposure limits (OELs) have not been established for the nanoscale form of the material through the traditional guideline or standards-setting agencies such as the Occupational Safety and Health Administration (OSHA), the ACGIH®, or the International Organization for Standardization (ISO). Because most existing occupational exposure assessment strategies presuppose the existence of such OELs, their absence for nanomaterials provides no regulatory motivation to conduct exposure monitoring. The limited routine monitoring efforts that do exist do not follow a consistent strategy.

These uncertainties have led to the use of control banding approaches to assessing risk levels and guidance for controls for nanomaterials in workplaces.[13,14] While control banding is useful in the interim, there is currently sufficient information available to facilitate the science-based development of an exposure assessment strategy using monitoring data for many nanomaterials. This article describes a highly tailorable exposure assessment strategy for nanomaterials that enables effective and efficient exposure management, (i.e., a strategy that can identify jobs or tasks that have clearly unacceptable exposures) while simultaneously requiring only a modest level of resources to conduct. The strategy is based on the strategy of the AIHA®, a generic framework that can be adapted for nanomaterials and that seeks to ensure that the risks to workers handling nanomaterials are being managed properly.[15] The strategy is focused on arriving at decisions based on collecting and interpreting available information.

Exposure Assessment Strategy

A flow diagram of the AIHA strategy is shown in Figure 1. The following sections provide more details of each step in the strategy.

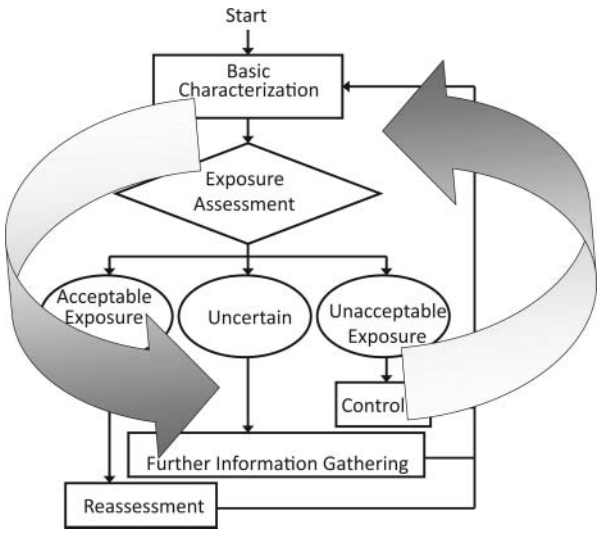

FIGURE 1. AIHA exposure assessment strategy

Basic Characterization

Workplace and Work Force

Basic characterization of the workplace includes collecting information on the workplace, work force, and environmental agents, as well as organizing information in a way that allows for efficient use by industrial hygienists. The industrial hygienist must identify the nanomaterials of concern; the sources of exposure for both engineered and incidental nanomaterials; and the processes, equipment, tasks, and work practices that can lead to potential for exposure to workers, as well as any workplace controls in place.

Understanding Exposure Potential from Processes

Processes leading to airborne nanomaterial releases could include vapor-phase synthesis reactors, heavy conveying or bagging operations, and shaping and grinding steps. Closed systems imply high levels of emission controls[16] with a low probability for exposure. Exposure potential may be higher when conveying or drying products, during reactor maintenance and cleaning, and during material handling tasks (e.g., bagging) when nanomaterials can become resuspended.[17–20]

In research laboratory settings, the quantities of nanomaterials handled may be smaller than in a production environment, but the numerous processing conditions and the wider variations in nanomaterial characteristics can make a proper assessment of exposure potential challenging, time-intensive, and costly. For example, Johnson et al.[21] found that sonicating hydrophobic carbon-based nanomaterials (CNMs) in deionized water suspensions results in airborne particle number concentrations lower than when handling dry CNMs. In contrast, sonicating hydrophilic CNMs in a moderately hard reconstituted water suspension containing natural surfactants dramatically increases airborne CNM particles compared with the handling of dry CNMs. Similarly, the presence of functionalized nanoparticles, the type of process, and the surfactants used may also affect the potential to become airborne.

Traditionally, industrial hygienists have used professional judgment that has been developed through experience and training to assess the potential for exposure to occur. However, these previous examples suggest that even subtle differences in nanomaterial characteristics may potentially change their exposure potential, and thus, the previous experiences of the industrial hygienists may not be applicable and may cause biases leading to erroneous assessments. For example, relying on an obvious visible dust source to recognize the potential for exposures may not be an appropriate indicator for nanomaterial exposure. For this reason, transient and spatial monitoring of occupational exposures may be required.

Characterizing Nanomaterials

It is important that the industrial hygienist have accurate information on nanomaterial characteristics. Frequently, information provided by the manufacturer or processor can be limited or misleading due to the ability of nanomaterial characteristics to change as they are added to or modified by other processes. Processing and handling steps can significantly alter nanomaterial characteristics, i.e., a dry nanomaterial powder dispersed into a liquid solvent may not have the same particle size distribution in the liquid form as it did as a dry powder.

In the case of airborne releases, nanomaterials may agglomerate and grow to much larger sizes.[22] Agglomeration of nanoparticles is a challenge for exposure assessment. If measurements are made close to the source immediately after release, a greater concentration of nanoparticles will be observed compared with measurement made at locations farther away or sometime after release. This should dictate the types of measurements made at various locations. Obviously, instruments capable of detecting particles in the nano size range would be needed at locations near the source. But it is easy to dismiss the need for instruments capable of detecting larger-sized particles, since they are not nanosized. Neglecting the presence of these larger agglomerates may sometimes incorrectly estimate the true health risk levels because some agglomerates may disaggregate into smaller components once deposited in the lungs or onto the skin. An aggregate may have a biologically relevant nanostructure. Methner et al.[23,24] have developed a nanomaterial emission assessment method to determine exposure potential to engineered nanomaterials.

In addition, many material safety data sheets (MSDSs) for nanomaterials do not distinguish between nanomaterials and their bulk counterparts. Emphasizing the distinction between non-nano and nanosized versions of a given material is key to good industrial hygiene practice. To understand nanomaterial characteristics, there must be good communication between the scientists and engineers who manufacture, process, and handle the nanomaterials and the industrial hygienists.

Background Particles and Incidental Nanomaterials

While identifying the sources, it becomes necessary to distinguish between engineered and incidental nanomaterials

and background aerosols. Background aerosols can be either naturally occurring or incidental if they are not caused as a result of any occupational activity, i.e., diesel exhaust from vehicles on a nearby road. Incidental nanoparticles caused by occupational processes must be included in any assessment of occupational environments. This requires an understanding of both the location and generation of nanomaterials and non-nanomaterials in the workplace, material handling tasks that can produce incidental nanomaterials, work practices and procedures, and material transfer. Investigation of other potential co-contaminant particle sources is also required, and professional judgment may also be needed to determine if these are causes for concern with respect to subsequent measurements. Combustion and high temperature sources, whether process- or non-process-related, should be particularly noteworthy. The incidental nanomaterials typically are not the focus of the exposure assessment. However, in sufficiently high concentrations, these incidental particles may also be considered a mixed exposure,[20] since these particles may not be without their own adverse health risks. While these particles may be in the same size range as the engineered particles of interest, they are difficult to distinguish definitively using common real-time instruments.[25,26] Sometimes, the concentration of incidental nanomaterials vary across space and time during the process tasks of interest and can be heavily influenced by intermittent, incidental sources (e.g., exhaust from propane or diesel forklift driving by, heating units, cleaning processes, or outside particle sources, such as vehicular exhaust that penetrates indoors). In such instances, correcting for incidental nanomaterials by simply subtracting a baseline value may induce significant error.

To control for potential variability in situations such as found in research laboratories, the background aerosol (including incidental nanomaterials from other occupational processes) is often measured before processes start, during processing, and then after tasks are completed.[21] As an example, Bello et al.[27] studied particle concentrations during chemical vapor deposition (CVD) growth and subsequent handling of vertically aligned carbon nanotube (CNT) films over the course of 6 months using a real-time fast mode particle sizer (FMPS) to measure number concentration of aerosol particles in the range 5.6 to 560 nm, a condensation particle counter (CPC) to measure total particles concentration from 10 nm to 1000 nm, and thermophoretic and electrostatic precipitators to evaluate particle size and morphology. During each session, continuous information was collected on particle number concentration of the background air during the whole cycle of the furnace operation: furnace heating, CNT growth, furnace cool-down, opening of furnace, removal of the substrate, and mechanical removal of CNTs from the silicon substrate. In a study of an automotive grey iron foundry, Evans et al.[28] measured ultrafine particle number and respirable particle mass concentrations in outdoor aerosol background levels, incoming make-up air, and non-process-related ultrafine concentrations as relevant background concentrations.

Thus, accounting for the background and incidental nanomaterials can be accomplished in several ways that are often situation specific. Options include measuring nanomaterial concentrations before or after the process, measuring outdoor ambient concentrations, and measuring at the intake of some processes that may or may not be from the outside. Measurements can be made simultaneously with process-related monitoring or pre- and post-process monitoring.

Exposure Assessment

Exposure assessment is a multi-step process conducted using the basic characterization data as input. In this assessment, the industrial hygienist begins by defining similarly exposed groups (SEGs) of workers based on knowledge and observations of the workplace, work force, and work operations. A critical assumption in such a classification is that workers within each SEG have similar exposure distributions. If SEG creation is done correctly with sufficient understanding of the workplace and with thoughtful follow-up and validation, this technique can become a critical element of an effective and efficient exposure risk management program.

Construction of Similarly Exposed Groups (SEGs)

Most commonly, classifying workers into SEGs or exposure zones is done on the basis of an a priori observation and understanding of the processes and tasks in which each group of workers are engaged and the likelihood of exposure to contaminants. [15,29,30] A key feature of this approach is that exposure monitoring data are not needed initially for defining the zones. This classification of workers is a subjective exercise that relies heavily on the professional judgment of the industrial hygienist.

This approach is useful in initial SEG or exposure zone construction. However, the professional judgment of most industrial hygienists is currently calibrated to visual cues related to particle mass concentrations that may not be reliable for infrequently used aerosol concentration metrics, such as number and SA, which may be critical for nanotechnology. Thus, it is advisable to obtain area- or job task-related measurements of mass, number, and SA concentrations metrics and to understand the relationships among them in these workplaces before determining SEGs. This will lead not only to better understanding of workplace factors that affect engineered nanomaterial emissions but also will help calibrate the professional judgment of hygienists to these newer metrics. Two useful tools proposed for this purpose are concentration mapping and job task-related measurements. Thus, the creation of SEGs or exposure zones for engineered nanomaterials should be a combination of subjective professional judgment and measurements.

Concentration Mapping

Concentration mapping is a technique to illustrate spatial and temporal variability of the aerosol concentration distribution in a workplace as a function of work processes. This technique can be applied to identify contaminant sources and as a

quantitative tool to prioritize implementation of cost-effective engineering controls[25,31] to investigate temporal variability and non-process-related particle sources[26] or as a pre-survey tool to determine sampling locations for aerosol concentration measurements.

Mapping can be utilized to help determine similar aerosol concentration areas (that can loosely correspond to SEGs) within a workplace. Park et al.[32] made measurements using several exposure metrics in a restaurant and in a die casting plant to compare the spatial distributions of particle number, SA, and mass concentrations and rank exposures in different areas. Spatial distributions and ranking of particle concentrations in different areas were different depending on the concentration metrics. Also, average concentration by job location in these mapping measurements showed different rankings depending on the selected aerosol characterization metric.

Ramachandran et al.[33] and Heitbrink et al.[34] reported similar findings from multiple-metric sampling studies conducted in facilities where incidental nanomaterials were generated. Designating SEGs appropriately based on correct information is important both for routine aerosol characterization assessment that serves as the basis of decision making regarding aerosol management, and future occupational epidemiologic studies to investigate any relationship between health effects and engineered nanomaterial concentrations.

To produce concentrations maps, the workplace is divided into a grid based on its size. To reduce temporal variability, an entire set of mapping measurements should be completed within a short time period. If battery-powered monitoring instruments are placed on a portable cart, potentially, 60 grid points could be measured in 2 hr given 1–2 min per sampling site. The grid resolution can be tailored to the situation to obtain finer resolution near suspected generation sources and areas of high occupational activity and a coarser grid for areas farther away.

Mapping measurements should be obtained several times to assess temporal variability. Arithmetic average concentrations can be used to construct the final particle maps. Color-coded contour plots can be generated and used to construct an easy-to-read concentration map and to help visualize the nanomaterial concentrations by different metrics using mapping software (e.g., Surfer 8.0; Golden, Colo., as used by these authors).

Workplaces may be categorized into two types from the perspective of the need for mapping measurements: production and laboratory. Production workplaces often have regular work, materials handling, and processing schedules and minimal changes in nanomaterial characteristics that permit a mapping approach. Laboratory workplaces feature irregular and less predictable work schedules, very broad and frequent changes in nanomaterial characteristics, and diverse procedures that are typically batch and small-scale operations and are not as amenable to the mapping approach. Therefore, aerosol monitoring in the lab workplace can be focused on the aerosol-generating task.

Pilot plant facilities typically have characteristics of both laboratories and production workplaces, and determining the best strategy for these work settings must be considered on a case-by-case basis. If the process is sufficiently long and stable, particle measurements at several locations would be helpful to understand how particles are distributed spatially. Otherwise, task-based monitoring may be more feasible. In this situation, simple line plots for all metrics can be constructed that show the concentration metrics by process, thus providing an intermediate version of concentration mapping.

Mapping can also help in understanding the evolution of the aerosol due to agglomeration as it moves away from the source and in determining an appropriate exposure assessment strategy. Areas close to a nanoparticle source are more likely to have a greater concentration of freshly generated nanoparticles compared with areas farther from the source that will contain aged aerosol with different size characteristics. This will have a significant effect on the definition of exposure zones based on different exposure metrics and the types of measurements made at various locations. The study by Ramachandran et al.[33] showing differences in diesel exposures for three job groups—bus drivers, bus mechanics, and parking garage attendants—is primarily due to the agglomeration of diesel exhaust aerosol, with the mechanics being exposed to fresh exhaust while the bus drivers and parking garage attendants are exposed to aged aerosol.

Mapping may be too labor-intensive to be routinely used in industrial hygiene.[28] However, mapping techniques can be a useful tool for the pre-survey phase of an exposure assessment. Visual aerosol maps can convey spatial information for aerosol contaminants effectively, locate unexpected sources of contaminants, and help prioritize control measures.[28] As a more detailed sampling strategy is formed, initial estimation of exposure levels from mapping can be used to establish sampling filter change schedules and to check if test site concentration levels are compatible with the operating ranges of the test instruments.

The mapping approach is limited in that it is based on short-term and area sampling. Thus, exposure estimation of each area based on the mapping measurements alone may not suffice. The aerosol monitoring results for mapping cannot be a substitute for personal sampling.

Job Task-Related Measurements

Personal breathing zone measurements can be used to assess short-term, task-based exposure intensity, which in turn can be used to evaluate the efficacy of exposure controls. The distance from the source for the task will affect the degree of agglomeration and, therefore, the definition of SEGs or exposure zones. As with concentration mapping, one should account for the background incidental particle concentration.

Prioritization of SEGs

It may not be feasible or necessary to carry out detailed exposure monitoring for SEGs that may have trivial exposures. However, the identification of such SEGs requires the

use of a screening tool. Tools such as the control banding approach proposed by Paik et al.[14] or the AIHA prioritization approach[15] may be useful. Both these approaches use a risk ranking scheme based on exposure and health hazard rating to arrive at a risk band that can be the basis of prioritization. While such screening tools are obviously attractive, they need to be used with caution as they have not been thoroughly validated for nanomaterials.

Exposure Metrics

If the workplace aerosol had only one mode and was reasonably homogeneous (i.e., the geometric standard deviation of the particle size distribution was low), then we would expect a high degree of correlation between particle number, surface area, and mass concentrations. However, in many situations the workplace aerosol has multiple modes. Typically, the large particle mode has fewer particles that contribute heavily to the aerosol mass, and the ultrafine particle mode contains a large number of small particles that do not contribute much to the mass. The correlation between mass concentration and number concentration (and surface area) may be poor in such instances. While mass concentration has traditionally been the metric for exposure assessment of airborne particles and is the basis for regulation, it may not always be appropriate for nanomaterials. Health risk assessments based on mass concentration as the exposure metric could underestimate ultrafine particle toxicity since these particles do not contribute significantly to total mass concentration despite their high numbers. While some studies have suggested particle number concentration as a more health-relevant metric than mass concentration,[12,35] others have shown particle surface area as being related to health outcomes[36] and a biologically more relevant metric due to the enhanced potential for surface reactivity for nanoparticles.[37–40]

However, from a workplace monitoring or detection perspective, transient increases in particle mass corresponded most closely to the release of nanoscale powders into the workplace atmosphere through manual handling and transfer operations.[20,22] Despite production-scale quantities, on a particle number or count basis the contribution from engineered nanomaterials can be relatively small compared with background or other particle sources.[20] Currently, no scientific agreement exists for appropriate exposure metrics for nanoscale particles.[14,41]

In epidemiologic studies as well as in routine industrial hygiene exposure assessments, groups of workers are split into SEGs as previously described. If exposure concentration by a less relevant exposure metric is used to determine exposure categories, workers could be misclassified into incorrect categories resulting in weaker exposure-response associations[42] or inappropriate exposure control and management decisions.

Since the question of the correct exposure metric is still a matter of debate, as an interim strategy for measuring airborne engineered nanomaterials, it is advisable to obtain area or job task-related measurements of all metrics and to understand the relationships between mass, number, and SA concentrations in workplaces. This will lead not only to better understanding of workplace factors that affect engineered nanomaterial emissions but will also calibrate the professional judgment of hygienists to these newer metrics. In addition, using the multimetric approach with additional air quality information, multiple ultrafine/fine particle sources and their relative contributions may be differentiated so that a more thorough understanding of the workplace may be gained.[20]

In the studies reported in the peer-reviewed literature, peaks of SA concentrations or fine particle number concentrations typically correlate better with the location of nanomaterial generation sources than mass concentrations. Rankings of aerosol concentrations (highest to lowest) may be different depending on the metric chosen. Thus, mass concentration, regarded in the practice of industrial hygiene as a standard aerosol concentration metric, cannot be a substitute or surrogate for SA or fine particle number concentration. At the same time, fine particle number and SA concentrations generally follow similar trends.

Another aspect of the aerosol characterization metric is the time averaging of measurements. At present, there is not sufficient biological evidence to determine whether acute (short-term) or chronic (longer-term) exposures are more health relevant. Short-term aerosol measurements permit identification of potential particle release points, thus informing process control improvement efforts. Therefore, it is appropriate to measure aerosol concentrations on both time scales in the interim. In light of these points, it is recommended that measurements of airborne particle mass, SA, and number concentrations be conducted using real-time instruments. There is value in maintaining both the time averaged results and the real-time data points for these metrics to enable future evaluations of the information.

Direct-Reading Instruments

Nanoparticle mass, surface area, and number concentrations can be measured directly or calculated through measurements of the particle size distribution. While there are a number of research-grade, benchtop instruments capable of measuring aerosol properties with high accuracy, such as a scanning mobility particle sizer (SMPS), these are not the focus of our recommendations because they are typically not field portable. Rather, we focus attention on commercially available instruments that can be used by industrial hygienists in exposure management. The instruments described in brief below and listed in Table I are easily portable and relatively inexpensive, thus facilitating their use in routine industrial hygiene monitoring. Additional information regarding the principles of operation for each device can be found in texts such as by Baron and Willeke[43] and ACGIH.[44] For each class of instruments, there are several manufacturers available. The instruments mentioned here are to be taken only as examples and not as endorsements of a particular product.

Direct-reading instruments possess an electronic optical device capable of transforming a signal produced by a particle or particle cloud into a recordable measurement as it is being

TABLE I. Properties of Portable Nanoparticle Measuring Devices

Instrument	Metric	Particle Size[A]	Concentration Range
Photometer	Mass	$0.1 \leq 10.0\ \mu$m	0.001–150 mg/m^3
Condensation particle counter	Number	0.01– 1 μm	0–100,000 #/cm^3
Optical particle counter	Size distribution by number	0.3 – >5 μm with 6 channels	0–3000 #/cm^3
Diffusion charger	Surface area	0.01$\sim$ >1 μm	0–10,000 μm/cm^3

[A]Range of particle diameters for which instruments of this type are responsive.

taken, and thus allow for "real time" monitoring of nanoparticles in the workplace. By their nature, such instruments are useful in understanding the temporal variability within a location or a task-period. These instruments have typically been designed to measure one of the three metrics: number, surface area, or mass. They can also vary in terms of how accurately a metric is determined relative to the size of the particles measured. Optical-based instruments are relatively inexpensive when compared with other sizing methods but suffer the drawback of measuring a particle based on its optical properties rather than the physical property of interest. The optical properties of the particles measured during an exposure assessment may not always be known; therefore, inaccurate measurements may result.

Because, by definition, a nanoparticle has at least one dimension <100 nm, it would be most beneficial if these instruments could accurately measure particles within that size range. However, an assessment of an occupational setting in which nanoparticles or nanomaterials are created may not necessarily reveal only particles <100 nm. As mentioned earlier, one may expect that locations near a nanoparticle source may have higher concentrations of particles < 100 nm, while somewhat farther locations will have lower concentrations due to agglomeration.

For example, at a CNT production facility, Baron et al.[45] found it difficult to reaerosolize the bulk material and measured a wide distribution ranging between 4 nm and 20 μm. Likewise, Peters et al.[22] discovered that nano-structured lithium titanate particles formed spherical aggregates with diameters between 200 nm and 10 μm. However, some field studies utilizing an SMPS with accurate size discrimination in the nanometer range have revealed a predominance of nano-sized particles. Demou et al.[46] measured nanoparticles in an industrial pilot plant and determined that the highest concentrations were associated with particles between 160–200 nm. Park et al.[47] measured silver nanoparticles in a manufacturing facility that ranged only between 30–40 nm when measured immediately after opening a process hatch door. These studies suggest that exposures in a nanoparticle production facility are not necessarily limited to <100-nm particles, and that instrumentation should be available to measure a wide range of particle sizes to fully evaluate workplace exposure levels. Agglomerates of nanoparticles may still have nano-sized features that may have potential health risks.

Given the need for a broad-ranging evaluation of aerosols in a nanomaterial production facility, an industrial hygienist may be required to utilize several instruments that together are capable of providing information on the full range of particle diameters present. For example, optical particle counters (e.g., HHPC-6, Met One, Grants Pass, Ore., or PDM 1.108 GRIMM Technologies, Inc., Douglasville, Ga.) typically measure size and number concentration of particles in the size range of 0.3–20 um with a concentration range of 0–2000 particles/cm^3. Condensation particle counters (e.g., CPC Model 3007, or P-Trak Model 8525, TSI Inc., Shoreview, Minn.) are real-time, single-particle counting instruments that measure particle number concentrations with the most accuracy between 10–1000 nm, with a concentration range of 0–100,000 particles/cm^3. Air drawn into a saturator tube is mixed with isopropyl alcohol vapor to become supersaturated. Then the aerosol is passed into a condenser tube where particles grow such that they are detected by a photodetector as they pass through a laser beam.

Both an OPC and CPC can be acquired as hand-held devices, but there are limitations to their use for evaluating nanoparticle exposures: the OPC can size-separate particle counts but cannot measure below 300 nm; the CPC can measure accurately between 10–1000 nm but does not size separate. Regardless, they can be utilized for real-time field measurements, including qualitative area sampling to determine the relative changes in size and number concentration, locate point sources, and validate engineering controls. Furthermore, if an OPC and a CPC are used together, an additional channel of particle counts between 10–300 nm can be obtained by subtracting the OPC counts between 300–1000 nm from all CPC counts, which span 10–1000 nm. Such an approach was followed by Peters et al.[22] and Evans et al.[28] in which an OPC and CPC were used in tandem when performing activity-based monitoring of workers in nanomaterial facilities. Schmoll et al.[48] evaluated this technique and found that it was relatively accurate as long as the particle type evaluated did not have a refractive index that differed significantly from that of the PSL spheres used to calibrate the OPC.

Portable aerosol photometers (e.g., DustTrak, Model 8520, TSI Inc., or pDR100 DataRAM, ThermoScientific Inc., Waltham, Mass.) may also be used to evaluate conditions in nanomaterial production plants. These instruments provide estimates of mass concentration using light scattering. The

sampled air passes through a chamber illuminated by a laser light. Light scattered by particles is measured using a photodetector. The intensity of the scattered light is a function of the particle mass concentration, the size distribution of the aerosol, and the composition of the aerosol. Aerosol photometers provide estimates based on an assumed density and particle size distribution that may be different when investigating nanomaterial sources. Photometers are typically sensitive to particles between 0.3 (300 nanometers)–10 um, with a concentration range from 0.001–150 mg/m^3. However, given their sensitivity range, they will only detect nanoparticles if they have agglomerated to >300 nm. An advantage to their use is related to their ability to provide a very fast response (~1 s) to changes in concentration and their small size favorable for personal sampling.

Although not of a size considered strictly a nanoparticle, particles with nanoscale features consisting of much larger overall dimensions (e.g., a fiber bundle with thickness much greater than the nanoscale but with individual fibers with nanoscale dimensions) need to be considered when assessing worker exposure. In such instances, the nanoscale features might retain some of their toxic potential despite the particle agglomerate or aggregate being much larger than a nanoparticle. Evans et al.[20] used a photometer in an evaluation of carbon nanofiber (CNF) production and found that respirable mass, measured with a photometer equipped with a respirable cyclone, most closely corresponded to carbon nanofiber release, suggesting the nanofibers consisted of larger particles. They also concluded that respirable mass measured with the use of a photometer was the most useful and practical metric for monitoring CNF exposures. Optical-based instruments are relatively inexpensive when compared with other sizing methods, for example, but suffer the drawback of measuring the optical diameter of the particle rather than a physical property related to particle transport, which in turn determines respiratory deposition. The optical properties of the particles measured during an exposure assessment may not always be known.

Diffusion chargers (e.g., nanoparticle surface area monitor, NSAM Model 3550, or AeroTrak 9000, TSI Inc. or the DC2000CE from EcoChem Analytics, League City, Texas) are used to measure the surface area of nanoparticles. The sampled air passes through a corona ionizer for ionizing where positive ions attach to the surface of the particles from the sampled aerosol by diffusion. The charged particles go through a Faraday cage inside an electrometer filter where the particles and charges are collected and the electric current is measured. The current is related to the surface area concentration. These instruments are typically accurate within a size range of 10–1000 nm and some (e.g., the NSAM and the AeroTrak 9000) have an instrument response that has been calibrated such that the current is proportional to the surface area concentration of lung-deposited particles based on the International Commission on Radiological Protection lung deposition model for a reference worker[49] and, therefore, provide a measure of the lung deposited dose.

However, the influence of particles over 400 nm on the calculated lung deposited dose is not known, and it is suggested that the instrument be limited to aerosol environments with limited particle counts between 400 and 1000 nm.[50] Ku and Maynard[51] evaluated the response of a diffusion charger relative to measures of surface area provided (indirectly) by an SMPS and transmission electron microscope (TEM) and found good agreement for particles but only for those smaller than 100 nm. Although diffusion chargers have been developed to be portable, they have not been used in published surveys of nanoparticle production facilities to date.

Time-Integrated Measurements

Laboratory analysis of longer-term samples, such as with scanning electron microscopy (SEM) or transmission electron microscopy (TEM), are useful in determining elemental composition and morphology of the particles, as well as detecting particles (e.g., fibers) too small to be seen by other means. They are also valuable to help interpret the real-time instrument data, particularly to help make judgments on the meaning of the real-time measurement particle size and source of the nanomaterials being measured. For example, a sample obtained near a nanomaterial source can be analyzed to obtain a clear signature of the nanoparticles based on elemental composition, size characteristics, and morphology. An air sample taken concurrently with a real-time sampler can then be used to determine the percentage of all particles in a given size range, measured by a real-time sampler, that are derived from the nanomaterial source. Once this relationship is firmly established, subsequent real-time samples can be used by themselves to determine concentration of the specific nanomaterial without a concurrent microscopy sample.

In situations (e.g., very near a source) where there are no particles from other sources in the same size as the nanomaterial source, the SEM and TEM measurements provide a useful validation of the real-time measurements. When employing electron microscopy methods, representative specimens of bulk source materials of the engineered nanoparticles or source area air samples in proximity to areas can be obtained for reference purposes. The source particulates can be analyzed to identify unique characteristics that can be used to establish material-specific analysis protocols. The challenges in such measurements are the same as for any kind of time-integrated measurement method, e.g., the need to collect enough material on the substrate to be above the limit of detection for the analytical methods; the need not to overload the substrate to makes microscopy difficult.

Multiple sampling methods can be used to yield a specimen suitable for TEM or SEM analysis. Open-faced filter sampling is arguably the easiest and most straightforward method. Polycarbonate (often preferred especially for SEM studies) or mixed cellulose ester filters can be used to perform an initial sampling study. Sampling techniques such as electrostatic or thermal precipitators are also available to collect particles for TEM or SEM evaluation.

Samples can also be obtained using size-selective sampling devices (for example, cyclones, elutriators, and cascade impactors) to deposit particulate on impaction substrates. Size-selective sampling may be desirable for separating airborne particles to evaluate different size fractions of materials in air. Since both SEM and TEM use a very small portion of the sample collected on the substrate, it is important to ensure that the analyzed portion is representative of the collected sample. Some of the newer samplers are designed to provide a uniform deposit of the aerosol on the substrate, thereby minimizing one source of bias.

The nano-MOUDI impactor (Nano-Micro-Orifice Uniform Deposit Impactor, (Model 125A; MSP Inc., Minneapolis, Minn.) can be used to measure particle size distribution by mass or number and to obtain samples for chemical analysis or electron microscopy. This model collects particles ranging from >18 μm to 0.010 μm on 13 stages. Aluminum or polycarbonate substrates can be placed on each stage to capture particles in which the selected substrates can undergo electron microscopy and chemical analysis. Optionally, the substrates can also be weighed, although chemical analysis is typically far more sensitive than gravimetry. SEM, inductively coupled plasma (ICP) mass spectrometry, and carbon analysis can also be used for morphology and speciation.

Occupational Exposure Limits (OELs)

The next step in the exposure assessment process is the selection of an appropriate OEL. Typically, nanomaterial MSDSs list the same Chemical Abstracts Service (CAS) numbers as their bulk forms and, more significantly, the same OELs as larger particles. The OELs for non-nanomaterials of many substances may imply low risk. If the industrial hygienist is not alert, the same OELs could be used for nanomaterials that actually may have much higher potential toxicities than their bulk counterparts. Until OELs for nanomaterials are established, industrial hygienists must adopt a conservative approach and not assume that health and safety data for a non-nanomaterial would also hold true for its nanoscale version. Except for a few prominent examples, most nanomaterials have no OELs, necessitating the development of ad hoc OELs for exposure management purposes. The Appendix describes several approaches to the development and adoption of ad hoc OELs for CNTs that could be developed by analogy with other OELs.

Such an approach is quite feasible in the absence of legal exposure limits and should be adopted to facilitate exposure management. It requires close attention to current literature on nanomaterial toxicity and reasoning by analogy to develop exposure limits. Of course, there is a high degree of uncertainty in ad hoc OELs. If the uncertainty in the OEL is high, the industrial hygienist can use large safety factors to ensure that the risk is not underestimated. The above approach is intended only as an illustration of the methodology for arriving at ad hoc or in-house OELs that may be usable until more definitive and legal OELs are established.

Defining the Exposure Profile

The final steps in the exposure assessment process are the characterization of exposure for the SEG and a comparison of the exposure to the appropriately selected OEL while simultaneously taking into account the uncertainty of both. A detailed description of the methods for characterizing exposure profiles and the associated statistical analysis is available in standard texts, such as Ignacio and Bullock.[15]

In the case of exposure to nanomaterials, professional judgment may not be adequate due to lack of experience of industrial hygienists in assessing exposures using new and unfamiliar metrics. Therefore, it is recommended that monitoring data be the mainstay of exposure assessment for nanomaterials. The monitoring data should be used to determine the 95th percentile of the exposure distribution relative to the OEL and thus determine into which of the four categories the exposure profiles falls.

Our knowledge of the variability of nanoparticle concentrations in limited at this point. In general, the number of samples required should be related to the variability of the exposures. The AIHA strategy suggests that 6–10 measurements be collected for most SEGs that are to be evaluated using exposure monitoring. Each measurement is taken over an averaging time interval relevant to the OEL. For example, if the OEL has an 8-hr averaging time, then 6–10 (8-hr average) measurements need to be obtained for analysis. For nanomaterial measurements made using real-time instruments, it is advisable to make measurements over the time period of the task or process or over the entire shift if needed at intervals of $\sim$5 sec and then use these data to obtain averages over larger time intervals. The real-time data can also be used to understand within-task or within-exposure-zone temporal variability. However, the recommendation for 6–10 measurements assumes that the underlying variability within a SEG is not excessive (geometric standard deviation, GSD$< \sim$3.5). If the GSD is greater, then it is an indication that the SEG is not well formed and there may be some exposure misclassification. In such instances, the original SEG may need to be split into two or more SEGs, each with a GSD that is not excessive.

Follow-Up and Control

As the previous sections indicate, the assessment of exposure to nanoparticles in a complex environment where there are other exposures also present is challenging. The occupational hygienist has to understand the potential for exposure from an understanding of the processes, exposure control mechanisms in place, and monitoring data. The basic characterization of the workplace and the task under consideration, and the formation of SEGs using concentration mapping based on actual monitoring data can then be used to determine whether detailed environmental characterization is necessary or is expected to be fruitful.

SEGs are prioritized for follow-up and control based on their estimates of exposure and acceptability and the uncertainty associated with those estimates. Of course, poorly controlled exposures are given priority for control (low uncer-

tainty) or further information gathering (high uncertainty) with possible addition of short-term controls. Lowest priority is given to SEGs with low exposure estimates made with low uncertainty. Different institutions or companies may have different control steps they may take depending on the location of the 95th percentile in terms of the exposure limit.

CONCLUSION

It is clear that there is considerable uncertainty about the metric that should be used for characterizing exposure intensity of nanoparticles (e.g., number concentrations, surface area concentrations, mass concentrations), and the health-relevant time interval over which exposure should be measured. The absence of well-defined OELs as well as a lack of understanding of available instrumentation also hinders exposure monitoring efforts.

This article is an effort to present a systematic approach to assessing and managing exposures to nanomaterials in workplaces. We recommend a "multi-metric" approach by which, to the extent possible, number, surface area, and mass concentrations are all measured over process duration and over the longer term. In evaluating nanoparticles released by a process, we need to account for ambient and non-process sources of other nanoparticles via monitoring before, during, and after the process. Occupational hygienists should not rely on professional judgment to assess exposures. The formation of SEGs should be based on monitoring data. Presumptive SEGs based on personal observations should be confirmed by measurements. It cannot be assumed that an OEL for a large particle version of a material is appropriate for the nanoparticle version of the material.

This article provides useful guidance on conducting workplace characterization, understanding exposure potential to nanomaterials, handling background aerosols, constructing SEGs, selecting appropriate instrumentation for monitoring, determining appropriate choice of exposure limits, and evaluating criteria by which exposure management decisions should be made. The exposure assessment strategy for nanomaterials is highly tailorable to most situations and workplace environments and enables effective and efficient exposure management while simultaneously requiring only a modest level of resources to conduct. The strategy is focused on arriving at decisions based on collecting and interpreting the available information. This article is intended as a practical guide for industrial hygienists for managing nanomaterial risks in their workplaces.

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APPENDIX—EXAMPLE SHOWING THE DEVELOPMENT OF AD HOC OELS

As the key criterion for making distinctions between exposures that are excessive and those that are not expected to result in adverse health effects, selection of the OEL is a critical and required step in the exposure assessment process. The acceptability of a given exposure cannot be resolved without selection of an OEL unless an exposure concept such as "As Low as Reasonably Achievable" is adopted.

There are well-developed methodologies by which formal OELs can be established.[52] Before an OEL can be established, several conditions must be met:

(1) The criteria for exposure assessment need to be established (e.g., what aerosol fraction and what exposure metric is most health relevant).
(2) The exposure assessment strategy should specify the need for short-term or long-term exposure measurements.
(3) The instrumentation and analytical methods for measuring these metrics should be available.
(4) A dose-response relationship should be established by means of toxicity data and quantitative risk assessment.

Of these four needs, only the instrumentation and analytical methods (Condition 3) are generally available for most nanomaterials; thus, very few nanomaterials have specific OELs. Exceptions include amorphous silicon dioxide with an OEL in Germany[53] and titanium dioxide with a proposed draft OEL from NIOSH of 1.5 mg/m^3 for fine and 0.1 mg/m^3 for ultrafine as time-weighted average concentrations for up to 10 hr/day during a 40-hr workweek.[54] Schulte et al.[52] suggest that there may be value in considering titanium dioxide to be representative of a whole class of poorly soluble, low toxicity dusts. Bayer MaterialScience derived an in-house OEL of 0.05 mg/m^3 for its multi-wall carbon nanotube (MWCNT) product (Baytubes) based on subchronic inhalation studies on MWCNTs.[55] Nanocyl utilizes an OEL of 0.0025 mg/m^3 for MWCNTs for an 8-hr/day exposure.[56] The German Federal Institute for Occupational Safety and Health (BAuA) published a risk-associated exposure limit for respirable biopersistent particles of toner containing a large fraction of nanoscale particles equal to 0.06 mg/m^3.[57] More recently, NIOSH has proposed a recommended exposure limit (REL) of 0.007 mg/m^3 for CNTs.[58] Beyond these exceptions, most nanomaterials have no OELs. How can exposure management be accomplished in the absence of such limits?

One way forward is to adopt a very conservative approach to "benchmark levels," which has been developed for four classes of nanomaterials by the British Standard Institute.[59]

- For insoluble nanomaterials, a general benchmark level of 0.066 ×OEL of the corresponding microsized bulk material (expressed as mass concentration) is proposed. This factor of 0.066 is in line with the potency difference of microscale and nanoscale titanium dioxide as described by NIOSH.[54]
- For fibrous nanomaterials, a benchmark level of 0.01 fibers/ml is proposed. This level is derived from the current limit value in asbestos removal activities in the U.K.
- For highly soluble nanomaterials, a benchmark of 0.5 × OEL is proposed.
- For carcinogenetic, mutagenic, asthmagenic, or reproductive (CMAR) nanomaterials, a benchmark level of 0.1 × OEL of the corresponding microsized bulk material (expressed as mass concentration) is suggested.

The Institute for Occupational Safety and Health of the German Social Accident Insurance[60] recommended benchmark limits for an 8-hr work shift that can be used for monitoring the effectiveness of protective measures in the workplace. They were careful in stating that these were not health-based exposure limits but rather were aimed at minimizing exposure. The benchmarks proposed were 20,000 #/cm^3 for biopersistent granular materials (metal oxides, others) with a density greater than 6000 kg/m^3, 40,000 #/cm^3 for biopersistent granular materials with a density less than 6000 kg/m^3, and 0.01 fibers/cm^3 for CNTs.

Many companies and chemical manufacturers have internal ad hoc exposure limits for chemicals that they develop. A similar approach is feasible to develop ad hoc OELs for nanomaterials, where available toxicity information on a nanomaterial can be used to develop an ad hoc OEL. The health effects information collected during basic characterization can be used for establishing an OEL. In this process, input is needed from toxicologists, occupational physicians, and epidemiologists in this process. The following paragraph describes how an ad

hoc OEL for CNTs could be developed by analogy with other OELs.

There is no clear epidemiologic evidence of health effects due to exposure to CNTs, although there is strongly suggestive evidence from animal studies. An excellent review of toxicological studies involving the respiratory route of exposure to CNTs is given by Pacurari et al.[61] Other studies have focused on the dermal route.[62–66] These studies suggest that CNTs are potentially toxic and produce a range of pulmonary health effects, including fibrosis, inflammation, formation of granulomas, and decreases in pulmonary function and dermal effects, including inflammation. Thus, there is sufficient reason to focus on the potential health effects of possible occupational exposures to single-wall carbon nanotubes (SWCNTs) and MWCNTs. Given this state of knowledge, it is important to set ad hoc exposure limits that can be used as guidelines in the absence of legal limits. One reasonable approach relative to CNTs is to consider existing OELs for other fibers that have some similarities to CNTs as anchor points.

Two physical attributes provide for limited comparison between CNT and refractory ceramic fibers (RCF) that have an established OEL—transverse fracturing and bulk solubility of RCF fibers that result in more fibers of decreasing length.[10] Likewise, MWCNTs have been shown to be structurally similar to chrysotile asbestos,[67] and Muller et al.[68] demonstrated that MWCNTs were capable of inducing inflammation and biopersistence in a way similar to that of asbestos. Based on similar physical attributes for CNTs, RCFs, and asbestos fibers, several OELs can be used to develop an ad hoc OEL for CNTs. For asbestos fibers >5 μm in length, NIOSH recommends a REL of 0.1 fiber per cubic centimeter of air (0.1 fiber/cc), as determined by a 400-L air sample collected over 100 min and NIOSH Method 7400.

For RCFs, the NIOSH REL and the ACGIH threshold limit value (TLV®) can be used. The NIOSH REL of 0.5 fibers/cc is intended to prevent the development of lung cancer, mesothelioma, or impaired pulmonary function. The REL applies to airborne RCF with dimensions length (L) $>$ 5 μm, fiber diameter $>$ 3 μm, and aspect ratio (AR) $\geq$ 5:1. The ACGIH TLV is 0.2 fibers/cc and is intended to prevent impairment of pulmonary function or fibrosis. The TLV applies to airborne RCF with dimensions L $>$ 5 μm, and AR $\geq$ 3:1.

As mentioned by Pacurari et al.,[61] the relationship between CNT length, diameter, and toxicity has not been fully examined to substantiate an asbestos-like pathological response. They cite the work by Shvedova et al.[69] who found differences in the fibrotic response to CNTs from that of asbestos and suggest that the tendency for SWCNTs and MWCNTs to bundle may have important toxicological consequences. This leads to an alternative approach for the development of an OEL based on the similarities between CNTs and crystalline silica.

A study that compared SWCNT with cytotoxic and non-cytotoxic reference dusts[70] found that the pulmonary responses to SWCNT were closer to those induced by silica (cytotoxic) than by either graphite or carbon black (non-cytotoxic). Shvedova et al.[69] also demonstrated that CNTs were more toxic than crystalline silica. Lam et al.[71] therefore have suggested that an OEL for respirable CNT dust be no greater than 0.1 mg/m^3. Pauluhn[72] also advocates for an approach to an OEL for CNTs that considers the strong tendency for CNTs to form bundles and derived an OEL based on pulmonary overload as the basis for the sequence of events that lead to pulmonary inflammation. These calculations led to an OEL of 0.05 mg/m^3 for thin-walled Baytube MWCNTs. More recently, based on an extrapolation from subchronic in vivo toxicity studies in rodents, NIOSH has proposed a REL for CNTs of 0.007 mg/m^3.[58]

Based on the similarities in properties of CNTs, asbestos, and RCF, and similarities in potential health effects, we can propose an ad hoc exposure limit for CNTs of 0.1 fibers/cc as a time-weighted average for work shifts up to 10 hr, for CNT fibers with dimensions L $>$ 5 μm and aspect ratio $\geq$ 3:1. Schulte et al.[52] recently proposed a similar for CNTs, again arguing by analogy to asbestos.

Thus, both mass- and number-based OELs for CNTs have been proposed.