CHAPTER 2

Assessing and Managing Exposures to Nanomaterials in the Workplace

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Chapter Outline

Assessing Nanoparticle Risks to Human Health.
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2.1 A General Strategy to Assess Workplace Exposures

Exposure, in general terms, is defined as the intensity of a hazard (e.g., concentration of a gas or particle contaminant) at an appropriate interface between the environment and the individual (e.g., personal breathing zone for respiratory hazards) over a specific time interval that has biological relevance (e.g., 15 min for an acute adverse health outcome). Exposure assessment is the practice of inferring exposures for a group of workers based on a sample from the broader population. The goal of this chapter is to describe an assessment strategy that enables effective and efficient management of exposures to nanomaterials (i.e., a strategy that can identify jobs or tasks that have clearly unacceptable exposures) and requires only a modest level of resources to implement.

The American Industrial Hygiene Association (AIHA) presents a general strategy to assess exposures to hazardous agents in the workplace in this context (Ignacio and Bullock, 2006). This strategy is used by industrial hygienists to protect the health of workers worldwide. A flow diagram of the AIHA strategy is shown in Figure 2.1 as a multistep process.

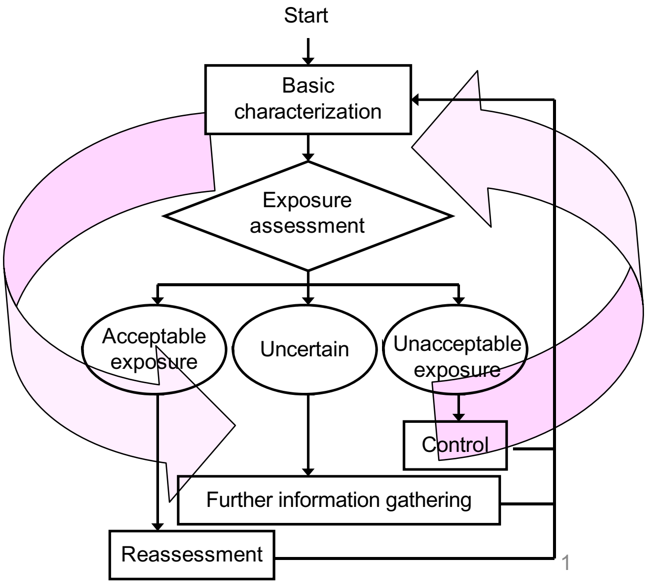

Figure 2.1
The AIHA exposure assessment strategy.

The first step is the *basic characterization* of the workplace, which includes collecting and organizing information on the workplace, workforce, and hazardous agents. The specific hazards (e.g., ergonomic hazards, chemical agents, and physical agents) and any controls (e.g., ventilation characteristics, use of personal protective equipment) are inventoried by workplace process and work task.

Next, this inventory is used to classify workers *a priori* into *similar exposure groups* (SEGs)—groups of workers anticipated to have a similar distribution of exposures. SEGs are defined on the basis of work similarity (similar profiles of job tasks), similarity of hazardous agents (similar chemicals to which they are exposed), and environmental similarity (ventilation characteristics, processes, etc.). The distribution of exposures for each SEG is then measured by using appropriate instruments, and these values are compared with an occupational exposure limit (OEL) with appropriate consideration of measurement uncertainty. On the basis of this comparison, exposures for the SEG are deemed acceptable, unacceptable, or uncertain. SEGs are then prioritized for follow-up and control, with SEGs having unacceptable exposures given high priority for control and those with uncertain exposures high priority for additional measurements. Low priority is given to SEGs with low exposure estimates made with low uncertainty.

This strategy is applied cyclically to achieve continuous improvement in the knowledge and control of exposures in the workplace. The tiered approach of ranking SEGs as having acceptable, uncertain, and unacceptable exposures enables focusing of resources on the most important issues. Available information is evaluated and used to conduct initial assessments of exposures and their associated uncertainties. Those initial assessments are then used to prioritize activities on the basis of the risks posed by the extent of the exposure and the extent of the uncertainty. Properly executing this strategy requires (i) an understanding of the workplace, workforce, and agents in the work environment; (ii) an understanding of potential exposures and at least an initial qualitative judgment on the potential sources likely to contribute to those exposures; (iii) mechanisms for understanding and appropriately resolving or managing uncertainty; (iv) mechanisms for driving appropriate follow-up to ensure that exposures are appropriately controlled; (v) mechanisms for documentation of all aspects of the process, results, and outcomes; and (vi) a structure that provides for prioritization and continuous improvement throughout.

2.2 Uncertainties Introduced by Nanotechnology

Nanotechnology is the manufacturing and application of materials and devices at the nanoscale (1–100 nm) enabled by the unique characteristics in the nanoscale, which are different from those in the macroscale. Engineered nanomaterials are materials with any external dimension in the nanoscale (<100 nm) or having internal structure or surface structure in the nanoscale. Nanomaterials can be classified as nano-objects and nanostructured materials. Nano-objects are materials with one, two, or three dimensions in the nanoscale and include nanoparticles (all external dimensions <100 nm), nanofibers (two similar external dimensions <100 nm), and nanoplates (one external dimension <100 nm). Nanostuctured materials are materials having internal nanostructure or surface nanostructure. Airborne nanoparticles are divided into two groups: (i) incidentally formed nanoparticles and (ii) engineered nanoparticles. Incidental nanoparticles, sometimes called *ultrafine particles*, are particles unintentionally produced during an intentional operation. Combustion, welding, metal processing, and emissions from diesel engines are examples of major sources of incidental nanoparticles. Engineered nanoparticles are particles designed and produced intentionally to have a certain structure and size, usually smaller than 100 nm.

Industrial hygienists face many uncertainties when the general exposure assessment strategy from the AIHA is applied to nanotechnology and nanomaterials. The first uncertainty is that nanotechnology processes are relatively new and not well documented like those in many traditional workplaces. A second uncertainty is that the same properties that make nanomaterials desirable from a manufacturing standpoint sometimes also make them more biologically active and toxic. Particles smaller than 50 nm may obey quantum physics laws instead of those of classic physics and in response may exhibit physicochemically unique optical, magnetic, and electrical characteristics. As the diameters of particles decrease to the nanoscale, the proportion of atoms or molecules on the surface increases rapidly. The increase in surface area often increases surface reactivity, with chemical bonds on the surfaces of particles being more unstable and reactive than those in the center. Thus, a higher proportion of atoms on the surface can allow a greater likelihood of interactions with biologically reactive groups that may cause further toxicity (Kreyling et al., 2006).

The understanding of health risks posed by most nanomaterials is, at best, limited. Key mechanisms for exposure processes and toxic effects of manufactured and incidental nanomaterials on humans remain poorly understood. Mechanistic uncertainties include those related to the following questions: (i) How long do manufactured nanomaterials persist in the atmosphere? (ii) How stable are nanomaterials over time, given specific occupational conditions? (iii) What is the effect of particle shape on their fate and transport? (iv) What are likely routes of exposure (e.g., inhalation, dermal, ingestion, and ocular)? (v) What are the metrics by which exposure should be measured (e.g., particle mass or number or surface area concentration)? (vi) What are the key mechanisms of translocation to different parts of the body after nanomaterials enter the body? (vii) What are the 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? (Kandlikar et al., 2007).

Much of what we do know from toxicologic studies suggests that many of the OELs developed for traditional exposures primarily consisting of fine and coarse particles may not be appropriate for exposures to the nanoscale form of a material. Most OELs are based on the metrics of mass concentration of particles in the "respirable" or "inhalable" size range. Similarly, the U.S. Environmental Protection Agency regulates atmospheric particulate matter in National Ambient Air Quality Standards as the mass concentration of particles smaller than 2.5 µm ($PM_{2.5}$, fine particles) or smaller than 10 µm (PM_{10}, coarse + fine particles). Other metrics may be more appropriate for assessing nanoparticle exposures. To illustrate this issue, the size distribution of particles emitted from a diesel engine is shown by number and mass concentration in Figure 2.2. Most of the mass concentration of diesel exhaust is associated with particles in "accumulation" (sometimes referred to as the "fine mode") and coarse modes, whereas the ultrafine or nanoparticle mode typically contains the vast majority of the number of particles. Slight changes in operating conditions of a diesel engine can dramatically change the ratio of particle concentrations in different-sized modes. As a consequence, the number concentration of an aerosol is often poorly correlated with its mass. Moreover, the particles in different modes may differ in composition substantially from the fine-mode and coarse-mode particles.

This issue has been observed repeatedly in a variety of settings. For typical atmospheric aerosols, Kreyling et al. (2003) reported that nanoparticles account for less than 10% of the mass concentration of particles smaller than 2.5 µm in diameter ($PM_{2.5}$) but more than 90%

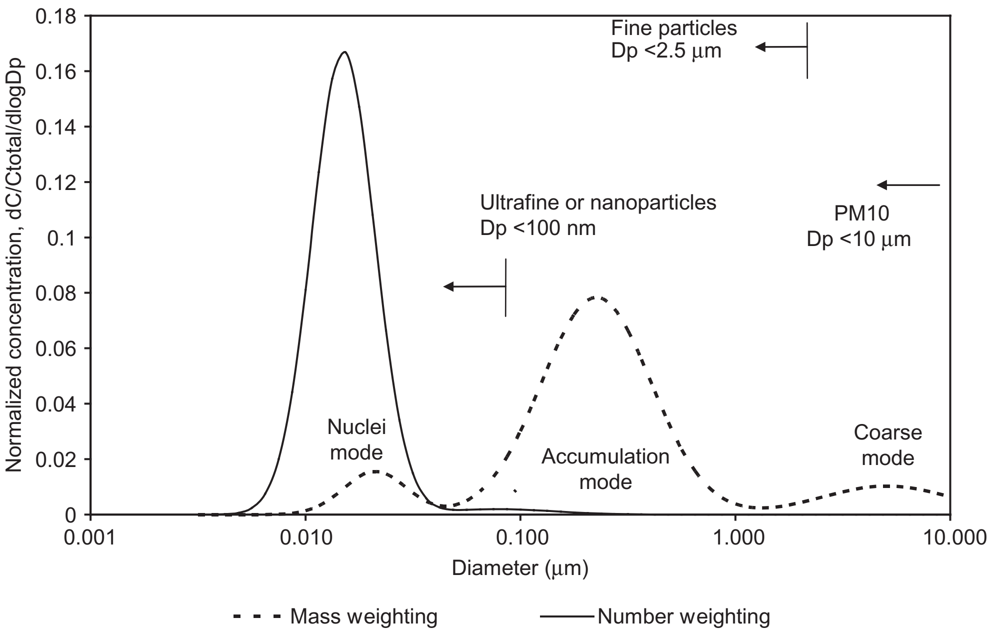

Figure 2.2
Idealized size distribution of diesel exhaust aerosol based on particle number and mass showing different modes. *Adapted from* Kittelson (1998).

of the number concentration. Heitbrink et al. (2009) found similar results for incidental nanoparticles in the automotive industry in the production of engines. For nanomaterials, high particle number concentrations may be present in the air despite very low mass concentrations. For example, a low concentration of 10 μg/m^3 of unit-density, 1-nm particles translates into ~19 × 10^9 particles/cm^3. The same mass concentration of 1-μm particles would amount to only 19 particles/cm^3 (a billion-fold difference). Likewise, the surface area concentration corresponding to 10 μg/m^3 of unit density 1-nm particles is 60,000 μm^2/cm^3, and for 1-μm particles it is 60 μm^2/cm^3 (a thousand-fold difference).

The absence of OELs for nanomaterials presents a problem for implementing the AIHA strategy for exposure assessment. Sampling and analytical procedures for measuring exposures to nanomaterials can be challenging and expensive. The net result is that exposure monitoring in occupational settings for nanomaterials is typically minimal or non-existent. When monitoring efforts are in place, they generally do not follow a consistent strategy but, rather, are executed in an ad hoc fashion. In the remainder of this section, we present what is known about potential routes of exposure and toxicity of nanomaterials. We then discuss OELs that apply to nanotechnology, with an emphasis on several new recommended exposure limits from the National Institute for Occupational Safety and Health (NIOSH) and benchmark exposure limits from Europe. Last, we discuss instruments that can be used to measure airborne personal exposures and area concentrations.

2.3 Exposure Routes

2.3.1 Inhalation

The fraction of particles that deposit in different regions of the respiratory tract depends strongly on particle size as estimated by a deposition model from the International Commission on Radiological Protection (ICRP), as shown in Figure 2.3 (ICRP, 1994). For particles larger than 100 nm, the predictions of the ICRP model have been experimentally validated by numerous studies, as reviewed by Vincent (2005). Although fewer studies are available, deposition measured experimentally for nanoparticles shows reasonable agreement with ICRP model predictions for the tracheobronchial and alveolar regions (Jaques and Kim, 2000) and in the extrathoracic (nasal) region (Cheng et al., 1996).

For particles larger than 300 nm, inertial forces and gravity settling dominate as the primary mechanism of deposition. Most >300-nm particles deposit in the head airways because inertial forces cause them to deviate from rapidly moving air and hit the mucus-laden walls. Inertial forces are, however, sufficient to cause some deposition of these particles in the tracheobronchial region. If particles in this size range pass to the alveolar region, they are often deposited due to gravity settling because the airflow is relatively slow and the residence time is long in the deep lung.

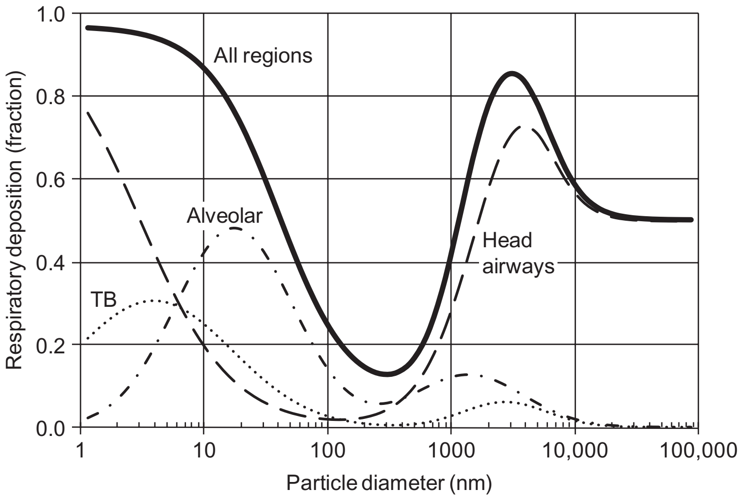

Figure 2.3

The fraction of particles depositing in the respiratory tract from 1 nm to 100,000 nm (100 μm) calculated using the regional deposition model from the ICRP (ICRP, 1994).

For particles smaller than 300 nm, deposition is dominated by the physical process known as *diffusion*—the net movement of a particle caused by Brownian motion. Superimposed on a particle's movement with flowing air, Brownian motion is an irregular wiggling motion imparted to the particle by the constant bombardment of air molecules, which increases with decreasing particle size. The fraction of particles that are deposited by diffusion can be expressed as the distance a particle moves due to diffusion divided by the airway dimension. Only the smallest particles have sufficient movement for deposition by diffusion in the relatively large airways and fast-moving air of the head airways (>20% for particles <10 nm) and the tracheobronchial region. The greatest deposition fraction for particles from 10 nm to 100 nm occurs in the alveolar region because air is slow moving and the alveoli are small (~200 μm in diameter). Particle deposition in the alveolar region peaks at approximately 20 nm because smaller particles are deposited in the upper airways before reaching this region and larger particles experience less movement by diffusion.

The respiratory system is able to clear particles, depending on where they are deposited. Particles that are deposited in the head airways are cleared by the mucociliary epithelium, which moves mucus and deposited particles toward the glottis, where they are swallowed (ingested). The tracheobronchial region is also covered with mucociliary epithelia that move the particles deposited in mucus upward toward the oropharynx (mucociliary escalator), where they are swallowed. Particles depositing in the alveolar region trigger an immune reaction in which alveolar macrophages engulf the particle and move it to the tracheobronchial region.

2.3.2 Dermal Exposure

There is considerable uncertainty about whether dermal exposure is a significant route of exposure for nanomaterials, as reviewed by Labouta and Schneider (2013). Cuts and lacerations can facilitate dermal penetration, many researchers such as Schulz et al. (2002), who studied the penetration of nanoparticles used in sunscreens, found little penetration of particles through an intact stratum corneum. However, penetration through the skin is influenced by nanoparticle characteristics (composition, surface coating, and geometry), skin characteristics, and situation (e.g., flexing of the skin). Monteiro-Riviere and Riviere (2009) showed that skin was permeable to some nanoparticles, especially quantum dot nanoparticles. The formulation of the nanoparticles that contact the skin can also influence the skin's permeability by altering its barrier properties. For example, dimethyl sulfoxide facilitates absorption of substances through the skin by removing much of the lipid matrix of the stratum corneum, leaving holes and shunts. Dermal absorption of nanoparticles does not appear to occur readily but can take place under certain conditions, and the factors dictating the extent to which absorption occurs are varied and complex. Researchers also caution that leaching of selected components of the particles through the skin and into the bloodstream is possible. Confounding these limited findings is the fact that different studies used different experimental protocols, making cross-study comparisons difficult.

2.3.3 Ingestion

Oral ingestion is likely to be an important exposure route. Studies have shown that nanoparticles are efficiently absorbed through the gastrointestinal tract (Jani et al., 1994) and that the particles then translocate through the mucosal tissue into the lymphatic and circulatory systems (Moghimi et al., 2001). Researchers have also found uptake of nanoparticles from ingestion of consumer products such as toothpaste and food additives (Fröhlich and Roblegg, 2012). The risk from accidental exposures to nanoparticles via this route, however, has not been not clearly demonstrated.

2.4 Occupational Exposure Limits

A generic exposure profile of concentrations measured every 15 min in the breathing zone of a worker over a work shift is depicted in Figure 2.4. These measurements are typically compared with OELs, which are based on prevention of the development of adverse health effects. The arithmetic mean exposure over the entire work shift (time-weighted average (TWA)) is compared with an OEL for contaminants with chronic adverse health effects, whereas individual 15-min measurements are compared with short-term exposure limits (STELs) for contaminants with acute adverse health effects. Several agencies and groups establish OELs: the Occupational Safety and

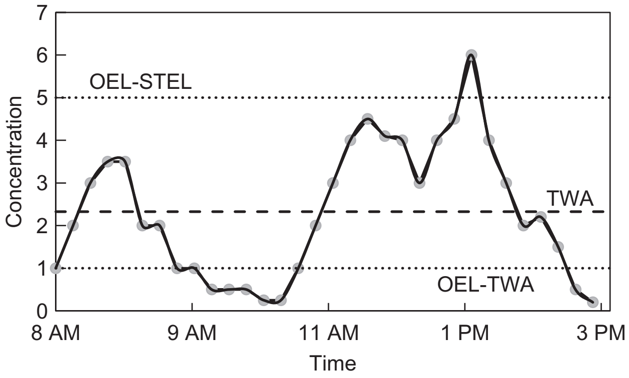

Figure 2.4
Generic exposure profile depicting concentrations measured every 15 min in the breathing zone of a worker over a work shift. The arithmetic average of all concentrations is the time-weighted average (TWA) exposure, which is compared with time-weighted average occupational exposure limits (OEL-TWA). Individual 15-min measurements are compared with short-term exposure limits (STELs).

Table 2.1 Example time-weighted average (TWA) occupational exposure limits (OELs) relevant to nanotechnology

Substance	Nanotech Application	OSHAPEL, mg/m^3	NIOSHREL, mg/m^3	ACGIHTLV, mg/m^3
Particles not otherwise regulated (PNOR) or specified (PNOS)	Many	15 (Total) 5 (Resp)	—	10 (Inhalable) 3 (Resp)
Barium, soluble	Batteries	0.5	0.5	0.5
Copper	Many	0.1 (Fume) 1 (Dust/mist)	0.1 (Fume) 1 (Dust/mist)	0.2 (Fume) 1 (Dust/mist)
Silver	Biocide	0.01	0.01	0.01
Platinum, soluble	Many	0.002	0.002	0.002
Titanium dioxide	Whitener, sun block	—	2.4 (Fine) 0.3 (Ultrafine)	—
Carbon nanotubes and fibers	Strength and electrical	—	0.001	—

Health Administration (OSHA) establishes permissible exposure limits (PELs), which are enforceable by law; the NIOSH establishes recommended exposure limits (RELs); and the American Conference of Governmental Industrial Hygienists (ACGIH) establishes threshold limit values (TLVs). Some TWA-OELs applicable to the nanotechnology industry are summarized in Table 2.1.

2.4.1 Permissible Exposure Limits from the OSHA

Although there are no enforceable PELs specific to engineered nanomaterials, the OSHA has established generic mass-based PELs that apply to airborne exposures in workplaces where nanomaterials are handled and produced. A PEL of 15 mg m^{-3} for total and 5 mg m^{-3} for respirable dust applies to particles not otherwise regulated (PNOR), based on the fact that the physical presence of biologically inert, insoluble, or poorly soluble, low-toxicity particles can overload the clearance mechanisms of the respiratory system. However, these PELs for PNOR are very high and of little practical value for most workplaces. Composition-specific PELs apply to some nanomaterials such as silver metal (0.01 mg m^{-3} for total particles). Workplaces establish compliance with these limits through filter-based sampling with gravimetric and/or chemical analysis.

2.4.2 Recommended Exposure Limits from the NIOSH

The NIOSH develops a current intelligence bulletin (CIB) to address limitations in PELs and the sampling methods that are used to show compliance to them. The CIB presents a quantitative risk assessment that includes dose-response relationships derived from available animal and human data. These relationships are used to establish RELs and assessment strategies to demonstrate that exposures are below these levels. RELs typically represent levels that over a working lifetime are estimated to reduce risks of adverse health outcomes to below 1 in 1000.

In the published CIB for titanium dioxide (TiO_2) (NIOSH, 2011), the NIOSH describes that an unknown number of U.S. workers produce and handle an estimated 1.5 million metric tons of TiO_2, which is incorporated into a wide variety of commercial products, including paints, cosmetics, and food. Exposures to TiO_2 in the workplace fall into the category of general dust (i.e., PNOR) with a PEL of 15 mg/m^3. Some of this material is unintentionally or intentionally produced in fine or ultrafine (nanoparticle) size fractions to achieve characteristics favorable to manufacturing or product performance. Scientific evidence suggests that persistent pulmonary inflammation and lung tumors scale with the particle size and surface area concentration of TiO_2 exposures. The NIOSH therefore proposed RELs for TiO_2 on the basis of the size of the particles in the air: 2.4 mg m^{-3} for fine TiO_2 and 0.3 mg m^{-3} for ultrafine (including engineered nanoscale) TiO_2. These RELs are for time-weighted average concentrations for up to 10 h per day during a 40-h work week. The NIOSH further recommends that exposures be controlled to as low a level as possible below these RELs. In the CIB, the NIOSH further suggests that these adverse health effects may not be material specific but result from a generic effect of poorly soluble, low-toxicity particles in the lung.

The NIOSH also published a CIB for carbon nanotubes and nanofibers in the workplace (NIOSH, 2013). An REL of 1 μg m^{-3} (8-h time-weighted average work shift exposure during a 40-h work week) for carbon nanotubes and nanofibers measured as elemental carbon by NIOSH Method 5040 to prevent excess risk of pulmonary inflammation and fibrosis.

The risk assessment presented in the CIB suggests that workers may have >10% excess risk of developing early-stage pulmonary fibrosis if exposed at the REL for a full working lifetime. However, the REL was set as the limit of quantification of NIOSH Method 5040, which the NIOSH has selected as the best available method to assess exposures. This method is nonspecific for carbon nanotubes and nanofibers, as other sources of elemental carbon are possible in workplace settings. Consequently, the NIOSH encourages the development of more suitable sampling and analytical methods, which may include microscopic methods such as those used to assess exposure to asbestos.

2.4.3 Benchmark Limits

Groups worldwide have used a categorical approach to establish benchmark OELs for nanomaterials without adequate toxicologic information as summarized by (Pietroiusti and Magrini, 2014). Nanomaterials are placed into groups with similar properties (e.g., particle size, surface chemistry) and modes of action (e.g., overburden of respiratory clearance mechanisms, fibrotic development). Limits for the group are based on materials with similar properties and modes of action for which there is toxicologic information. In Table 2.2, a summary of benchmark OELs established by the German Institute for Occupational Safety

Table 2.2 Benchmark exposure limits for nanoparticles from the German Institute for Occupational Safety and Health (referred to as the IFA) in Germany and the British Standards Institute (BSI) in the United Kingdom

Nanoparticle Category	BSI (UK)	IFA (Germany)
Fiber-like		
• Rigid, biopersistent CNT	10^4 f/m^3	10^4 f/m^3
• Metal oxides	10^4 f/m^3	
• CNTs without asbestos-like effects		4×10^4 f/m^3
Biopersistent granular (density <6000 kg/m^3)		
• Titanium dioxide	0.066× WEL	4×10^4 p/m^3
• Carbon black, silica, fullerene, zinc oxide, dendimers, polystyrene, nanoclay	0.066 × WEL or 2×10^7 p/m^3	4×10^4 p/m^3
Biopersistent granular (density >6000 kg/m^3)		
• Cerium oxide, gold, iron, iron oxide, silver, cobalt, lanthane, lead, antimony oxide, tin oxide	0.066 × WEL or 2×10^7 p/m^3	2×10^7 p/m^3
With carcinogenic, mutagenic, asthmagenic, reproduction effects		
• Nickel, cadmium containing quantum dots, chromium VI	0.1 × WEL	2×10^7 p/m^3
• Beryllium, arsenic, zinc chromate	0.1 × WEL	4×10^7 p/m^3
Liquid and soluble	0.5 × WEL	WEL

CNT stands for carbon nanotube; WEL is the work exposure limit established as a regulatory limit based for non-nano material; f stands for fiber; p stands for particle.

and Health (referred to as the IFA) and the British Standards Institute (BSI). In many cases, the benchmark exposure limits are expressed in terms of number concentration (fibers or particles per unit volume of air). In others, the benchmark OEL is expressed as a fraction of the existing exposure limit for a compound.

2.5 Instruments Available to Assess Exposures

In traditional methods for measuring personal exposure to airborne particles, air within a worker's breathing zone is pulled through a filter mounted in a 37-mm cassette (open or closed faced), respirable sampler, or inhalable sampler. The mass concentration is then computed as the mass collected on the filter (determined gravimetrically or by chemical analysis). A variety of samplers and instruments have been developed or applied to assess workplace exposures to particles, including nanoparticles, by metrics other than total, respirable, or inhalable mass concentration. These commercially available instruments are affordable for many organizations, portable, and easily used by industrial hygienists in exposure management.

2.5.1 Direct-Reading Instruments

Number concentration

As summarized in Table 2.3, a variety of direct-reading instruments are available for measuring particle exposures by various metrics. The total number concentration of an aerosol can be measured with a condensation particle counter (CPC). In a CPC, workplace air is saturated with a working fluid (e.g., water, isopropyl alcohol) by drawing it through a wetted tube. The molecules of working fluid then condense onto the particles and cause them to grow by condensation. The particles are then counted individually as they pass through a

Table 2.3 Direct-reading instruments for measuring particle concentrations

Instrument Category	Output	Example Instruments
Condensation particle counter, CPC	Total number concentration from ~15 nm to ~1 μm	Hand-held: CPC 3007 and P-Trak (TSI Inc.); CPC 3800 (Kanomax) Personal: PUFP C100 (Enmont, LLC)
Optical particle counter, OPC	Number concentration by size from ~300 nm to ~10 μm	Hand-held: HHPC6 (Met One); PDM 1.108 (Grimm Technologies, Inc.)
Photometer	Mass concentration from ~300 nm to ~10 μm	Hand-held: DustTrak II 8532 (TSI Inc.) Personal: pDR-1500 (Thermo Sci)
Diffusion chargers	Varies by instrument, but generally surface area concentration of submicrometer particles	Benchtop: NSAM 3550 (TSI Inc.); Aerotrak 9000 (TSI Inc.) Hand-held: DC2000CE (Ecochem Analytics) Personal: Discmini (Matter Engineering)

laser-based optical detector. Hand-held CPCs vary by model but typically measure particles from 10 or 20 nm to >1.0 µm over a concentration range of 0 to ~250,000 particles/cm^3. Newer models have been introduced for personal measurement (Ryan et al., 2015).

Hand-held optical particle counters (OPCs) provide particle number concentration by size typically from ~300 nm to ~10 µm in multiple-sized channels. OPCs use light scattering to count and size particles. Sizing is accomplished on the basis of the fact that larger particles scatter proportionally more light in the forward direction than smaller particles. OPCs are able to detect only those particles that scatter a sufficient amount of light (typically >300 nm).

Mass concentration

Hand-held and personal aerosol photometers are available to measure particle mass concentration. Sampled workplace air passes into a "sensing volume," which is illuminated by light from a laser. The light scattered by the assembly of particles in the sensing volume is measured with a photometer at a discrete angle from the incident light (typically 90°). The intensity of the scattered light is directly related to particle mass concentration but is influenced by aerosol size distribution, shape, and composition. Photometers provide a direct readout of mass concentration and can be operated with a size separator on the inlet to provide respirable mass concentration, PM_{10}, $PM_{2.5}$ or other size fractions. Many photometers provide a built-in filter holder downstream of the detection region. The gravimetrically measured mass concentration measured with this filter over a time-integrated sample period is often used to adjust the highly resolved data from light scattering. This practice improves estimates of mass concentration from a photometer by accounting for effects of site-specific aerosol size, shape, and composition.

Surface area concentration

Hand-held and personal instruments based on diffusion charging are available to directly measure particle surface area concentration. In a diffusion charger, positive ions produced with an electrical corona attach to the surface of particles, and the charged particles are collected on a grounded filter. The electrical current draining from the filter and measured with a highly sensitive electrometer is related to the particle surface area concentration. Diffusion chargers can be operated in different configurations to provide estimates of the surface area concentration that would deposit in various areas of the respiratory tract. A bench-top nanoparticle surface area monitor (NSAM, TSI, Shoreview, MN, USA) can be configured to estimate the surface area concentration that would deposit in different regions of the lung (Asbach et al., 2009). A hand-held model (DC2000CE, EcoChem Analytics, League City, TX, USA) outputs total surface area concentration and has been evaluated for use in workplace environments (Vosburgh et al., 2014). A personal model (DiSCMini) outputs for surface area concentration and particle number concentration of deposits in the lungs (Mills et al., 2013).

2.5.2 Time-Integrated Measurements

Detailed characterization

Several types of devices can be used collect workplace particles for subsequent analysis of size, morphology, and composition. Such information can help distinguish engineered nanomaterials from incidental nanoparticles or larger particles that are in the environment. With this information, the industrial hygienist is in a better position to devise routine measurement strategies and to interpret data from direct-reading instruments. For example, morphology can be analyzed using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), size classification can be achieved using TEM, and chemical composition of the particles can be assessed using TEM with energy dispersive spectrometry (EDS) (Peters et al., 2009).

Several instruments, both personal and hand-held, are available to collect particles directly onto substrates suitable for SEM or TEM. Particles can be collected onto filters amenable for SEM (polycarbonate or mixed cellulose ester) using traditional samplers (e.g., open-faced cassettes, respirable, inhalable samplers), although the filter material makes analysis of nanoparticles challenging by TEM. Electrostatic (Miller et al., 2010) and thermophoretic (Thayer et al., 2011; Azong-Wara et al., 2013) precipitators are available to collect particles onto TEM grids that can then be easily analyzed by either TEM or SEM. When employing electron microscopy methods, representative bulk source nanomaterials should be collected to confirm the identity of engineered materials apart from other particles in the workplace. Electron microscopy is part of the assessment strategy recommended by the NIOSH to distinguish TiO_2 nanoparticles from larger TiO_2 particles and background particles collected with a respirable sampler.

The Nano-Micro-Orifice-Uniform-Deposition Impactor (NanoMOUDI) (Model 125, MSP Corporation, Shoreview, MN, USA) collects particles onto aluminum or polycarbonate substrates in 13 stages from 10 nm to >18 μm. The advantage of this instrument is that the substrates with collected particles can be analyzed gravimetrically, by bulk chemistry methods (e.g., ICP-MS), or by electron microscopy. Operation of the NanoMOUDI, however, requires considerable expertise in selection and proper handling of substrates, assembly and disassembly of impactor plates, and microscopic and chemical analyses.

Routine monitoring

Several researchers have developed personal samplers to collect nanoparticles apart from larger particles. Bulk chemical analysis (e.g., inductively coupled plasma mass spectrometry (ICP-MS)) of the collected nanoparticles can then be performed to directly measure engineered nanoparticle exposure. The continuity with traditional industrial hygiene sampling practices and dramatically lower cost of bulk chemical analysis compared with electron microscopy make these samplers amenable to routine monitoring of exposures to engineered nanoparticles.

The Personal Nanoparticle Sampler (PENS) simultaneously obtains samples for the respirable size fraction and nanoparticles (Tsai et al., 2012). In the PENS, respirable particles passing through a cyclone encounter a micro-orifice impactor that collects particles >100 nm. Nanoparticles are then collected on a Teflon filter. Similar to the PENS, the Nanoparticle Respiratory Deposition (NRD) Sampler (ZNRD001, Zefon International, Ocala, FL, USA) uses a respirable cyclone to sample workplace aerosol from within the breathing zone (Cena et al., 2011). A three-jet impactor removes particles larger than 300 nm, and smaller particles collect to eight nylon meshes, which collect the particles with an efficiency mimicking total deposition in the respiratory tract.

2.6 Specific "Best Practices" for Exposure Assessment Strategy in Nanotechnology

2.6.1 Basic Characterization

Workplace and workforce

Basic characterization by industrial hygienists includes the collection of information on the workplace, workforce, and environmental agents. For any workplace, this process includes an observational walkthrough to gather information on processes, tasks, and controls; a review of Safety Data Sheets (SDSs), previous sampling data, and process flow information; and interviews with supervisors and workers. The process flow patterns must be identified with an accounting of material transfer (e.g., raw material storage, dumping, conveying, and bagging), process output (e.g., intermediate or final products), and byproducts (e.g., cleanup operations, nanomaterials collected through ventilation controls, and waste streams). Process flow diagrams, facility schematics, and descriptions of the process with chemical reactions and standard operating procedures aid in carrying out this step. Information on the workforce, including the division of labor, the frequency of occurrence for tasks required of workers, and personal protective equipment (PPE) use, should be collected in this process. Sources of information include plant rosters and organizational charts, job and task descriptions, current job safety analysis, interviews with supervisors and workers, and detailed workplace observations.

Specific processes leading to direct airborne nanomaterial releases are important to consider in the context of nanotechnology facilities. These processes include vapor-phase synthesis reactors, heavy conveying or bagging operations, and shaping and grinding steps. Even for processes that are closed systems, these operations may require high levels of emission control (Swihart, 2003). In closed systems, unless there are unintentional leaks, the probability for exposure may be low. Exposure potential can be higher when products are being conveyed or dried, during reactor maintenance and cleaning operations, and other material handling tasks (e.g., bagging) when nanomaterials can become resuspended (e.g., Evans et al., 2010). In the case of airborne releases, nanomaterials may occur as agglomerates in the coarse size range (e.g., Peters et al., 2009). Ignoring these larger-sized particles in favor of nonagglomerates may sometimes lead to incorrect estimates of the true health risk levels because of the potential for some agglomerates to disaggregate into smaller components once deposited in the lungs or onto the skin. An aggregate may also have a biologically relevant nanostructure.

Workplaces in the production category often have regular work, materials handling, and processing schedules and minimal changes in nanomaterial characteristics, whereas research laboratories often feature irregular and less predictable work schedules. In research laboratories, the quantities of nanomaterials handled are typically smaller than in a manufacturing or production environment, but the numerous processing conditions as well as the subtle variations in nanomaterial characteristics can make a proper assessment of exposure potential challenging, time intensive, and costly. For example, Johnson et al. (2010) 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 handling of dry CNMs. Similarly, the presence of functionalized nanoparticles, the type of process, and the surfactants used may also affect the potential for CNM particles to become airborne.

Traditionally, industrial hygienists use professional judgment developed through experience and training to predict potential exposures. However, subtle differences in nanomaterial characteristics can potentially change their exposure potential, rendering such decisions based on professional judgement erroneous. For example, relying on an obvious visible dust source to recognize the potential for exposures may not be appropriate in the case of such small particles.

Initial characterization of the workplace should include identification of any potential background or occupational sources of incidental nanoparticles. The location and an estimate of emissions should be made for each potential source. Combustion and high-temperature sources, whether process or nonprocess related, are 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 because they may not be without their own adverse health risks.

Characterizing nanomaterials

The industrial hygienist must obtain accurate information on nanomaterial characteristics. Frequently, information provided by the manufacturer can be limited or misleading. On SDSs, many manufacturers do not distinguish nanoparticles from the bulk form of the same substance, listing the Chemical Abstracts Services (CAS) number and OEL for the bulk form. Moreover, the processing and handling steps can significantly alter nanomaterial characteristics. For example, the size distribution of a nanomaterial powder will often be altered when dispersed in a liquid compared with when dry. Thus, the industrial hygienist must understand the process flow and anticipate the characteristics of the engineered nanomaterial in this process through communication with scientists, engineers, and workers. It is advisable to analyze by electron microscopy samples of the nanomaterial at different stages in the manufacturing process. Images of particles from various processes can then be compared with those from analyses of airborne samples.

2.6.2 Construction of Similar Exposure Groups Combined with Exposure Assessment

SEGs are formed primarily on the basis of professional judgement of the industrial hygienist to increase efficiency of the exposure assessment and management strategy. A critical assumption in such a classification is that the workers within each SEG have similar exposure distributions. However, the professional judgment of most industrial hygienists is calibrated to visual cues related to particle mass concentrations that are often not reliable for number or surface area concentrations, especially for nanomaterials. As an interim strategy, concentration mapping and job-task-related measurements by number and mass concentration are recommended. These measurements can then be used to establish SEGs and strategies for routine monitoring.

Concentration mapping

Concentration mapping involves the measurement of particle concentrations by different metrics at many locations throughout a workplace with direct-reading instruments. The first step is to divide the workplace into a sampling grid based on its size. To minimize uncertainty introduced from temporal variability, an entire set of mapping measurements should be completed within a short period (e.g., 1–2 h) with a nominally 1-min sample obtained at each grid point. The monitoring instruments, placed on a portable cart, can then be moved to the next location in the next minute. Thus, around 60 grid points could be measured in 2 h. The spacing between sampling points can be determined as follows:

$$\frac{\text{Total area of a workplace (m}^2\text{)}}{\text{60 data points}} = \text{Basic measurement unit (m}^2\text{/point)} \qquad (2.1)$$

The grid resolution should be tailored to the situation to obtain finer resolution near suspected sources of generation and areas of high occupational activity and a coarser grid for areas farther away.

From the many instruments available (see Section 2.3), we recommend a CPC to measure total particle number concentration from ~15 nm to ~1 μm and an OPC to measure particles by size from 300 nm to ~10 μm. For each measurement point, an estimate of the sub-300-nm number concentration (usually a good indicator of nanoparticle concentrations) is made by subtracting the number concentration measured with the CPC by that measured with the OPC for bins ranging in size from 300 nm to 1 μm. An estimate of mass concentration can then be made by assuming a particle density by following Peters et al. (2006) or Park et al. (2010). 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 visualize the nanomaterial concentrations by different metrics with the use of mapping software (e.g., Surfer 8.0, Golden, CO, USA). This information can be used to visualize the spatial and temporal variability of aerosol concentrations in a workplace as a function of work processes. This technique can be applied to identify contaminant sources or as a presurvey tool to determine sampling locations for routine aerosol concentration measurements.

For example, Park et al. (2010) used concentration mapping to assess aerosol concentrations by various metrics in a die casting facility (see Figure 2.5 for schematic of facility and Figure 2.6 for hazard maps). Two light-scattering laser aerosol photometers (DustTrak Model 8520, TSI Inc., Shoreview, MN, USA) were used with size-selective inlets to measure the PM1.0 and respirable particle mass concentrations. A real-time CPC that counted single particles with diameters ranging from 0.02 to 1.0 μm was utilized for number concentration (P-Trak Model 8525, TSI Inc., Shoreview, MN, USA). A hand-held OPC (AeroTrak Model 8220, TSI Inc., Shoreview, MN, USA; or HHPC-6, Hach Ultra, Grants Pass, OR, USA) was used to simultaneously count particles >0.3 μm in diameter into six size bins (0.3–0.5 μm, 0.5–1.0 μm, 1.0–2.5 μm, 2.5–4.0 μm, 4.0–0.0 μm, and >10.0 μm). A surface area monitor (AeroTrak Model 9000, TSI Inc., Shoreview, MN, USA) was used for determining alveolar surface area concentration of deposited particles. Spatial distributions and of particle concentrations in different areas (loosely corresponding to SEGs) were different, depending on the concentration metrics chosen.

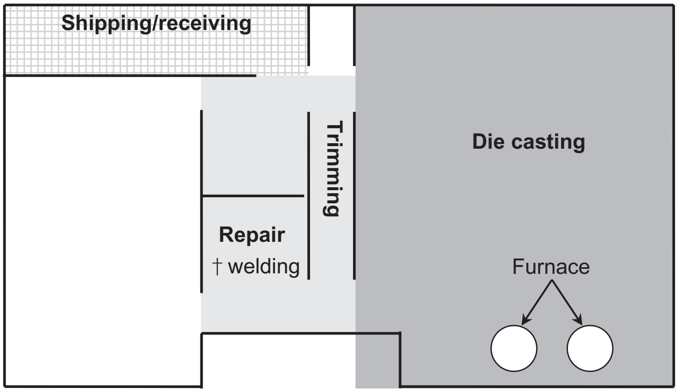

Figure 2.5
Schematic of die casting facility. *From Park et al. (2010).*

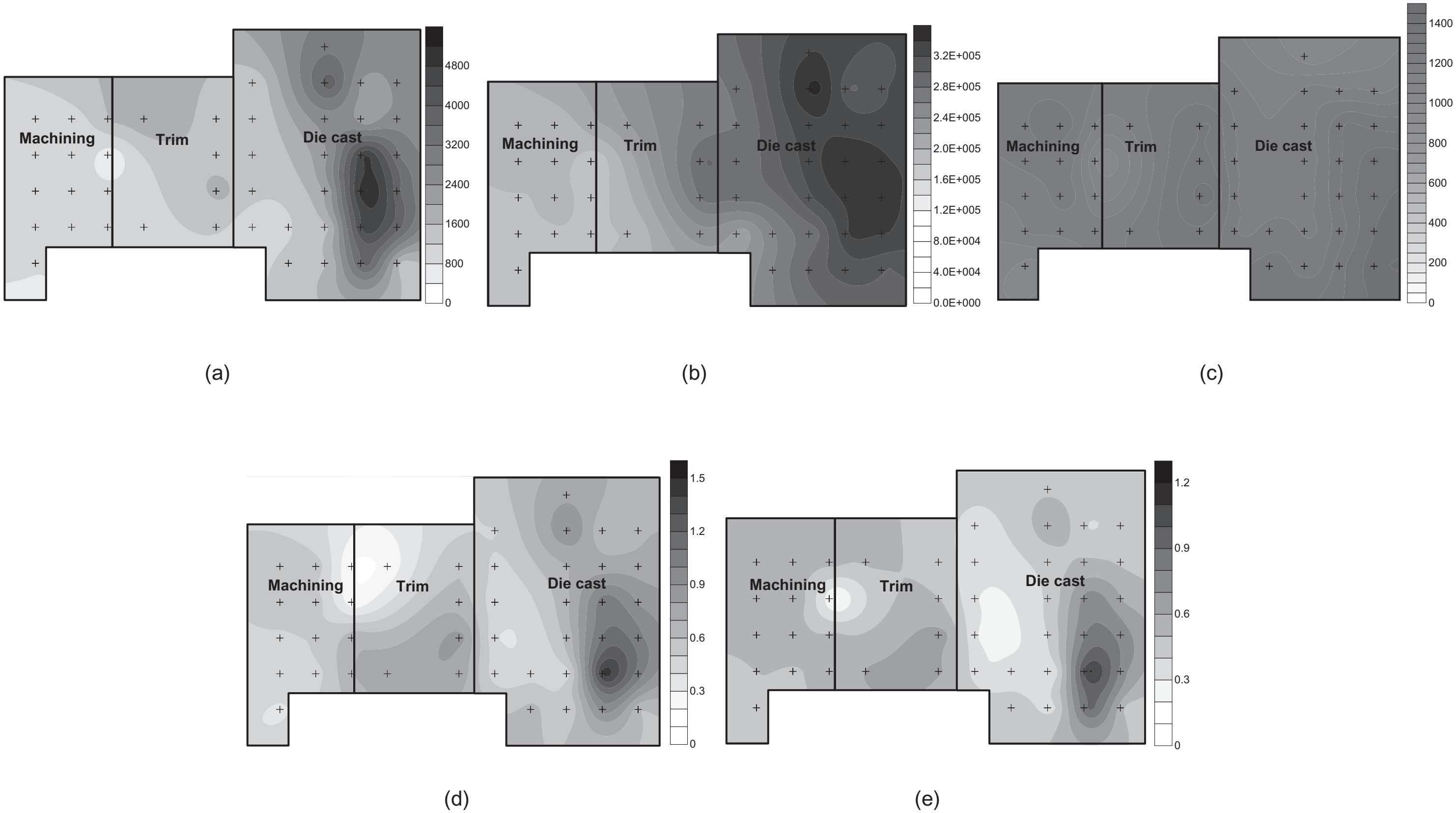

Figure 2.6

Particle concentration maps in the die casting factory (+: sampling location). (a) SA (μm^2/cm^3). (b) Fine particle number (particles/cm^3). (c) Coarse particle number (particles/cm^3). (d) Respirable matter (mg/cm^3). (e) PM 1.0 (mg/cm^3). *From* Park et al. (2010).

Job-task-related measurements

The same direct-reading instruments used in concentration mapping can be useful in characterizing exposures by tasks within a job. Here, breathing zone measurements are made during specific tasks, and relative particle measurements are used to identify potential sources or work methods that release higher levels of nanomaterials. This technique can be applied to identify short-duration contaminant sources and compare the relative effectiveness of work process control techniques in reducing exposure potential. It is also effective in identifying processes in need of exposure control activities based on comparative readings.

Background particles and incidental nanoparticles

Accounting for background and incidental nanoparticles is important and can be done in several ways, depending on the workplace. This process can be difficult when using only direct-reading instruments because incidental nanoparticles may be in the same size range as the engineered nanomaterial of interest. Sometimes, incidental nanoparticle concentrations also drift substantially for some 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 simple before, during, and after subtraction may be more challenging.

Options include measuring airborne particle concentrations with a process on and off, outdoors, and at air supplies. Methner et al. (2010) described a nanomaterial emission assessment technique (NEAT) to evaluate exposure potential to engineered nanomaterials, which is a qualitative approach that uses several direct-reading instruments. In the NEAT, the background aerosol is measured with the process (or task) on and off.

2.6.3 Interpretation of Exposure Assessment Results

Selecting occupational exposure limits

An appropriate occupational exposure limit (OEL) is needed to decide whether exposures are uncertain and require more measurement or are excessive and require control. There are well-developed methodologies by which formal OELs can be established (Schulte et al., 2010). 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 if one needs to measure short-term or long-term exposures.
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. Consequently, few nanomaterials have specific OELs except those mentioned in Section 2.4.

One option is to adopt conservative "benchmark levels" that have been developed for nanomaterials (see Table 2.2). Alternatively, many companies and chemical manufacturers develop internal ad hoc exposure limits for nanomaterials in the absence of legal exposure limits. Sufficient toxicologic information must be available, with inputs from toxicologists, occupational physicians, and epidemiologists. However, this process requires close attention to the current literature on nanomaterial toxicity and reasoning by analogy. 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 risk is not underestimated.

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 taking into account the uncertainty of both. Within each SEG, the workers have a distribution of exposures (i.e., the exposure profile of the SEG) that needs to be characterized. Characterizing an exposure profile requires an understanding of the statistics of sampling and the underlying exposure distribution, estimates of the exposure central tendency and variability, and some measure of the uncertainty in those estimates. A thorough knowledge of exposure variability and its characterization is critical for developing a proper sampling strategy and interpreting the results of sampling.

In addition to an estimate of exposure and its uncertainty for the SEG, outputs from the exposure assessment process include a decision as to whether or not the exposure is acceptable. Here again, it is useful and efficient to define exposure categories. Occupational exposure distributions are typically skewed to the right and are described quite well by the *lognormal probability distribution.* Acceptability is commonly evaluated by comparing an upper percentile such as the true group 95th percentile to the OEL. In the AIHA strategy, the 95th percentile of the exposure profile is estimated along with its upper confidence limit (UCL). Based on the magnitude of the group 95th percentile and its UCL relative to the OEL, the exposure is classified into one of four categories: "highly-controlled," "well-controlled," "controlled," or "poorly controlled" (Table 2.4). In the AIHA strategy, four categories are described, but there is no reason for not using other numbers of categories to better match the specific goals of the organization's exposure assessment strategy.

For conventional chemicals, the vast majority of exposure assessments are based primarily on professional judgment, with formal or informal input from associated exposure models. Even exposure assessments based on a wealth of monitoring data require professional

Table 2.4 Exposure category rating scheme. Exposure rating is assigned by comparing the 95th percentile exposure, $X_{95\%}$, of the exposure distribution to the full shift time-weighted average (TWA), occupational exposure limit (OEL), or short term exposure limit (STEL)

Exposure Rating	Control Zone Description	Qualitative Description	Recommended Statistical Interpretation
1	Highly controlled	Exposures infrequently exceed 10% of limit	$X_{95\%} < 0.10 \times \text{OEL}$
2	Well controlled	Exposures infrequently exceed 50% of limit and rarely exceed the limit	$0.10 \times \text{OEL} < X_{95\%} < 0.5 \times \text{OEL}$
3	Controlled	Exposures infrequently exceed the limit	$0.5 \times \text{OEL} < X_{95\%} < \text{OEL}$
4	Poorly controlled	Exposures frequently exceed the limit	OEL < 95th percentile

judgment to determine how the monitoring data are most appropriately used to assess exposure and to interpret any data analysis. In the case of exposure to nanomaterials, professional judgment may not serve us well because of the limited 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. Monitoring data should be used to determine the 95th percentile of the exposure distribution relative to the OEL and thus determine which of the four categories an exposure profile falls into.

The AIHA strategy suggests that six to ten measurements be collected for most SEGs that are to be evaluated using exposure monitoring (Ignacio and Bullock, 2006). Each measurement is taken over an averaging time interval relevant to the OEL. For example, if the OEL has an 8-h averaging time, then six to ten 8-h average measurements should be obtained for analysis. For nanomaterial measurements made using direct-reading instruments, it is advisable to make the measurements over the period of the task or process or the entire shift, if needed, in intervals of ~5 s, and then use the data from these short intervals to obtain averages over larger time intervals. For statistical analysis, the measurements should be obtained as randomly as feasible from workers, work shifts, and tasks. An underlying assumption is that the population of exposures does not change during the measurement period. Readings can be plotted as a time series as a subjective test of the stability of the exposure profile. The data can also be used to calculate simple descriptive statistics (i.e., mean, median, minimum, maximum, geometric mean, geometric standard deviation, and percentage of data above the OEL). Measurements can then be ranked and plotted as a cumulative distribution on log-probability axes. If the data fall on a straight line, then the underlying population of exposures is log-normally distributed. A W-test can be used as a more rigorous test of log-normality. The 95th percentile of the exposure distribution can then be calculated along with its upper confidence limit. At this point, a judgment about the acceptability or unacceptability of the exposure can be made.

2.6.4 Follow-Up and Control

As was illustrated in Figure 2.1, SEGs are prioritized for follow-up and control based on the estimates of their exposures, and the acceptability and uncertainty associated with those estimates. Of course, poorly controlled exposures are given priority for control (low uncertainty) 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 in place, depending on the location of the 95th percentile in terms of the four exposure categories.

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