

Occupational exposure limits for nanomaterials: state of the art

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Abstract Assessing the need for and effectiveness of controlling airborne exposures to engineered nanomaterials in the workplace is difficult in the absence of occupational exposure limits (OELs). At present, there are practically no OELs specific to nanomaterials that have been adopted or promulgated by authoritative standards and guidance organizations. The vast heterogeneity of nanomaterials limits the number of specific OELs that are likely to be developed in the near future, but OELs could be developed more expeditiously for nanomaterials by applying dose–response data generated from animal studies for specific nanoparticles across categories of nanomaterials with similar properties and modes of action. This article reviews the history, context, and approaches for developing OELs for particles in general and nanoparticles in particular. Examples of

approaches for developing OELs for titanium dioxide and carbon nanotubes are presented and interim OELs from various organizations for some nanomaterials are discussed. When adequate dose–response data are available in animals or humans, quantitative risk assessment methods can provide estimates of adverse health risk of nanomaterials in workers and, in conjunction with workplace exposure and control data, provide a basis for determining appropriate exposure limits. In the absence of adequate quantitative data, qualitative approaches to hazard assessment, exposure control, and safe work practices are prudent measures to reduce hazards in workers.

Keywords Nanomaterials · Regulation · Risk assessment · Occupational safety and health · Carbon nanotubes · Control banding

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Introduction

One of the major tools for prevention of occupational disease from exposure to specific agents is the use of occupational exposure limits (OELs). OELs for nanomaterials would be useful in reducing the health risk to workers exposed to engineered nanoparticles by providing risk managers and health professionals with a quantitative health basis for assessing the effectiveness of risk management practices (e.g., use of engineering controls). OELs have been established

for airborne chemical agents for almost 100 years (Cook 1945; Paustenbach 1998). They serve as benchmarks for assessing and controlling workplace exposures and for triggering the use of personal protective equipment (PPE) and implementing medical surveillance. OELs are established to minimize the likelihood of adverse effects occurring from exposure to a potentially hazardous substance. OELs are determined from the observation of workers exposed to the substance or from the results of laboratory animal studies.

For the most part, there have been no risk-based OELs established specifically for engineered nanomaterials because of limited toxicological data on only a few types of engineered nanoparticles. As the knowledge of the toxicity of nanoscale materials has accumulated, so has the awareness that mass-based OELs which exist for the larger form of the material known as “bulk” materials (i.e., larger particle sizes of a material of a given chemical composition) may not be appropriate for these same materials at the nanoscale. For example, evidence for carbon nanotubes (CNTs) (which are rolled sheets of graphene) and for ultrafine titanium dioxide illustrates that current OELs for bulk materials are not adequate for nanoscale variants of the same composition (Shvedova et al. 2005; Kuempel et al. 2006; Dankovic et al. 2007). That is, workers exposed to nanomaterials that are controlled to airborne mass concentrations indicated by OELs for their large-sized counterparts (e.g., graphite OEL applied to CNTs or total dust titanium dioxide OEL applied to nanoscale titanium dioxide) may not be adequately protective against disease. Consequently, there is a need to develop OELs specifically for individual or groups of nanomaterials. This task is made more difficult by the fact that the physicochemical properties of engineered nanoparticles and the operational parameters of the processes that create them are varied which may result in different toxic potential. The various physicochemical combinations are so large as to be impractical to assess toxicity and to develop an OEL for distinct nanomaterial variants. This does not mean that OELs for specific materials should not be developed. Rather it means that OELs may need to be developed for specific categories of nanomaterials with common hazard potential based on parameters such as molecular structure or physicochemical characteristics.

History of OELs

Overview

The concept of establishing airborne workplace exposure limits for potentially hazardous agents is based on the principle of establishing: (1) quantitative relationships between magnitude and duration of exposure to an industrial substance and the nature and the magnitude of the response of the worker, and (2) limiting airborne exposure to potentially hazardous agents to a concentration below which there is no significant threat to worker health (Paul 1989). This concept traces back to the late nineteenth and early twentieth centuries with the study of Gruber (1883) on carbon monoxide and Kobert (1912) on 20 industrial substances with toxic effects of acute exposure.

In the first 40 years of the twentieth century, the number of exposure limits rapidly increased (Sayers 1927; Lehman and Flury 1938; Paustenbach 1998). By the early 1940s, control of the occupational environment to prevent adverse health effects from hazardous substances was becoming an accepted principle. OELs have been developed by a number of organizations and government agencies and given different names (e.g., maximum allowable concentrations, threshold limit values, permissible exposure limits, recommended exposure limits (RELs), provisional hygiene standard) to reflect their intended use in the workplace (Illing 1991). To date, it is estimated that more than 6,000 OELs have been established worldwide (Paustenbach and Langner 1986; McHattie et al. 1988; Galer et al. 1992; Brandys and Brandys 2008).

The history of OELs includes not only their development but also their uses. The existence of an exposure limit does not necessarily imply that it will be protective for all workers. Originally, OELs were developed for employers or industrial hygienists to use at their discretion in the workplace (Paustenbach 1998). However, eventually OELs were incorporated in laws and consensus standards. When incorporated into laws (e.g., occupational standards), OELs are required to be used by the employer to control exposure (i.e., maintain exposures below the limit). An OEL is only one part of an occupational health standard or risk management process intended to minimize adverse health risks for exposed workers. Other parts of an occupational standard frequently

include other risk management requirements, such as engineering controls to reduce exposures, the training and education of workers, and the implementation of good work practices. OELs are also used to trigger the need for PPE (e.g., respirators) and the establishment of a medical surveillance program. Finally, the development and deployment of OELs also has led to the implementation of overall risk assessment practices for entire industrial processes.

The historical approach to setting OELs was generally based on observations of human experience in the workplace. If airborne concentrations of a substance were causing adverse health effects in workers, allowable exposure levels were reduced to a concentration that did not produce observable harmful effects (Greim and Zeigler-Skylakakis 1997; Ku 2000). By the middle of the twentieth century, toxicity testing of chemicals in laboratory animals had become more common and epidemiologic studies were conducted more frequently. Many OELs were based on the no-observed-adverse effect-level/safety factor (NOAEL/SF) approach (Ku 2000; van Leeuwen and Vermeire 2007). In this approach, all pertinent animal and human studies are reviewed and the highest dose that did not cause an adverse effect (NOAEL) was identified and a set of safety factors (e.g., 0.10 \times) applied to address the uncertainty in the extrapolation of effects observed in animals to humans (WHO 1994). This approach was based on the assumption that if exposure to a chemical was kept below some concentration (referred to as a threshold dose) no adverse health effects would be observed.

For carcinogens, a standard risk assessment method using animal chronic bioassay data has been to extrapolate to low risk levels (e.g., <0.1% is for a 45-year working lifetime) in humans by assuming a linear dose–response relationship without any threshold level for genotoxic carcinogens. Chronic bioassays with sufficient statistical power to detect effects at low exposures require a large number of animals. Such studies have become impractical and there is increasing need to use biomechanistic data, short-term *in vivo* or *in vitro* studies, and biomathematical modeling in risk assessment where feasible. The statistical model most often used in cancer risk assessment has been the linearized multi-stage model (LMS). The OEL is derived by selecting a concentration on the LMS curve that corresponded to some

level of acceptable risk. One limitation of the LMS model is that all carcinogens are treated the same way regardless of mode of action (e.g., direct- or indirect-acting genotoxicants). These broad types of carcinogen mechanisms are sometimes called threshold dose and non-threshold dose carcinogens, respectively (Ku 2000). In practice the identification of a threshold dose in a population has been difficult, and confidence interval estimates often include zero (Park and Stayner 2006).

An alternative approach for setting OELs for carcinogens and non-carcinogens is the determination of the benchmark dose (BMD) (Crump 1984; EPA 1996). The BMD is defined as the maximum likelihood estimate (MLE) of the exposure that produces some low level of risk derived from a statistical model. The BMDL is the 95% lower confidence limit (LCL) on the BMD. The BMDL is used as a point of departure (POD) to extrapolate to the target risk level. Linear extrapolation is used when the dose–response relationship is known to have a linear component below the POD or when the cancer mechanism is not known (EPA 2005). When sufficient data exist to conclude that the dose–response relationship is not linear at the low dose, then non-linear extrapolation can be used (EPA 2005). The benchmark approach is preferred over the uncertainty or safety factor approach for non-carcinogens because it utilizes all the dose–response data and provides a method to develop risk-based exposure limits (NRC 2008).

OELs for particulate matter and fibers

Historically, OELs for particulate matter have been in two broad categories: fibrogenic and non-fibrogenic. The units of measurements for particulates have varied over time with some fibrogenic aerosols, such as crystalline silica and asbestos, initially measured in units of millions of particles per cubic foot (mppcf) of air (Higgins et al. 1917; Cook 1987; Dressen et al. 1938) and more recently measured as mass per unit volume of air (e.g., $\mu\text{g}/\text{m}^3$ for crystalline silica) or as fibers per cubic centimeter (f/cm^3) of air (e.g., asbestos, fibrous glass). The general tendency for measuring non-fibrogenic aerosols has been the use of mass per unit volume of air (e.g., $\mu\text{g}/\text{m}^3$, mg/m^3).

Non-fibrogenic dusts that did not have specific established toxic effects were treated as “nuisance”

or “low toxicity” dusts with assigned OELs that were relatively “high”. In an early recognition of the significance of the smaller-sized fraction of dust that could reach the alveolar region of the lungs, the respirable fraction was assigned a separate value in the U.S., i.e., 15-mg/m³ total dust, 5-mg/m³ respirable dust). Over time, it was realized that the use of the term “nuisance dusts” for poorly soluble low toxicity (PSLT) dusts may be inappropriate to describe their inhalation hazards. These dusts were subsequently referred to by various organizations as Particles Not Otherwise Classified (PNOC) or Particles Not Otherwise Specified (PNOS). Epidemiological studies and long-term animal studies indicate that such a broad classification was not appropriate and that particle size may be a critical factor in influencing toxicity (ACGIH 2001).

OELs for dusts are often expressed as total dust and respirable dust. The criteria for respirable dust arose from two sources, the British Medical Research Council’s (BMRC) Criterion known as the “Johannesburg criterion” and the criteria from the 1961 Los Alamos Conference. The BMRC criterion relates to the mass of dust collected using a particle size selector which permits passage of particles with aerodynamic diameters of 9.2, 7.1, and 5.0 μm . The Los Alamos criterion uses aerodynamic diameters of <2, 2.5, 3.5, 5.0, and 10 μm . These criteria for respirable dust were selected to approximate the portion of the airborne dust that could reach the gas-exchange region of the lung (Cook 1987).

More recently, an international size-selective definition of respirable dust was developed through cooperation by the International Standards Organization (ISO 1995), the Comité Européen de Normalisation (CEN 1993), and the American Conference of Governmental Industrial Hygienists (ACGIH 1984). These definitions describe the probability that airborne particles, as a function of aerodynamic diameter, will enter (and therefore be capable of depositing in) the human respiratory tract. These definitions include the following particle size fractions: inhalable (capable of depositing anywhere in the respiratory tract), thoracic (capable of depositing in the lung airways), and respirable (capable of depositing in the gas-exchange region of the lungs).

Respirable dust sampling devices that operate in accordance with the international definition have a collection efficiency that is consistent with the

average fractional deposition of particles in the alveolar region of the human respiratory tract of healthy persons. According to deposition models, the mass-fraction of nanometer particles depositing in the respiratory tract is greater than that for larger respirable particles. Nanoparticles (<100-nm diameter) have a 30–99% probability of depositing in the human respiratory tract and 20–50% deposition in the alveolar region, according to average predictions for workers (ICRP 1994; ISO 2007). The deposition fractions are greater with mouth breathing and exercise.

Fibrous dust particles with an aspect (length to diameter) ratio greater than 3 to 1, are typically evaluated as the number of fibers per cubic centimeter of air. Fibers can be natural, synthetic, or mineral and much of the history of fiber-related research primarily grew out of the health and exposure issues regarding asbestos (Baron 2001). Critical in the health considerations of fibers in addition to dose are length, diameter, and biopersistence in the lung. As new information was developed, OELs for asbestos have been reduced from 5 mppcf in 1946 to the current OSHA standard of 0.1 f/cm³ (CFR 1910.1001; Cook 1987; Kamrin 1988; ACGIH 2009).

Quantitative risk assessment (QRA)

QRA methods can be used in setting OELs when adequate data are available concerning the relationship between the external exposure or the internal dose of a hazardous agent and an adverse response to that exposure in animals or humans. QRA provides estimates of the severity and likelihood of an adverse response associated with exposure to a hazardous agent (Piegorisch and Bailer 2005). When information is known about the route of exposure and mechanism of toxicity, physiologically based pharmacokinetic models can be used to extrapolate the dose administered in animal studies to humans (Travis et al. 1990; Kuempel et al. 2006). Quantitative risk estimates are used in conjunction with occupational exposure data to characterize the health and safety risk to workers, to form a basis for risk management decisions, and to evaluate the effectiveness of engineering controls and other occupational safety and health measures.

For engineered nanomaterials, it is likely that in the foreseeable future most QRAs will involve the extrapolation of animal data to humans. While ultimately epidemiologic studies are most useful, it is not likely that they will be available for some time (Schulte et al. 2009). In the meantime, there is an increasing amount of data from animal studies for some engineered nanomaterials that may be adequate for conducting a QRA (OECD 2008; Ma-Hock et al. 2009; Shvedova et al. 2009; Pauluhn 2010a, b).

Standard risk assessment methods can be used to estimate the working lifetime risk of an occupational disease from exposure to nanoparticles. These methods generally involve: evaluating the available data (dose–response data in animals), selecting the adverse response (non-reversible, clinically significant), determining the critical dose (e.g., BMD associated with a specified level of risk), calculating the human equivalent dose (accounting for species-specific differences such as target tissue volume or surface area, dose rate, and/or metabolism), and determining the working lifetime exposure concentration that would result in that dose (including consideration of deposition, uptake, and clearance) (Kuempel et al. 2006) (Fig. 1).

Selecting the data set

The ideal animal data set for estimating occupational respiratory disease risks in workers is generally a chronic inhalation study. Chronic exposure in animals (generally 104 weeks in rats) is treated as equivalent to a full (45 years) working lifetime

exposure in humans. While chronic studies are available for some nanoparticles such as titanium dioxide, carbon black, and diesel exhaust particulate, there are no published long-term inhalation studies involving engineered nanoparticles, particularly CNTs. To date, for CNTs, only subchronic studies involving 20–90 days of exposure are available (Drew et al. 2009; Ma-Hock et al. 2009; Pauluhn 2010a). Adjustment of study results from non-chronic studies in animals may be needed based on mechanistic understanding of the relationship between short- and long-term effects or to account for uncertainty in these mechanisms.

Critical dose

The term critical dose for inhaled particles or fibers is defined as the dose in the animal lung (usually the rat or mouse) associated with a specified response (e.g., inflammation, fibrosis, or lung cancer). A frequently used measure of critical dose is the BMD which is defined as the dose corresponding to a small increase (e.g., 10%) over the background level of response (Crump 1984). Both the maximum likely estimates (MLEs) of the BMD and its 95% LCL (BMDL) are determined by fitting statistical models to the dose–response data. The BMDL estimates can be derived either from a single model or an average of various models (Wheeler and Bailer 2007). Extrapolation to lower risk levels is achieved by model fitting or by linear extrapolation from the BMDL. In the U.S., a risk level for a severe disease (e.g., cancer) that is considered significant is 0.1%, or 1 case per 1,000 workers exposed for a 45-year working lifetime (US Supreme Court 1980).

Human equivalent dose

To obtain an estimate of the human-equivalent of the animal dose, consideration of species differences between animals and humans including differences in physiological and metabolic processes is required (Travis et al. 1990). For inhaled particles, the equivalent dose in rodents and humans may be estimated by adjusting for differences in the lung surface area (e.g., as particle dose per surface area of lungs). A default assumption in risk assessment (in the absence of specific data) is that an equivalent dose in animals and humans will result in an equal risk of

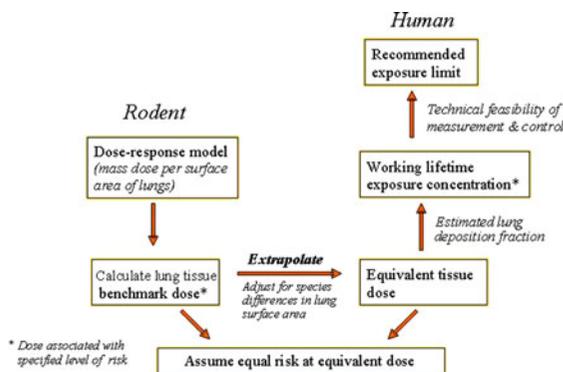


Fig. 1 Quantitative risk assessment methods in developing recommended exposure limits for inhaled particles

disease based on the assumption that the same mechanism of action is operating in both animals and humans. It is also appropriate to account for human variability in dose and response, including sensitive subpopulations to the extent that data are available. Risk estimation often utilizes information on variability in the animal data (for example, using the BMDL estimate); although, human variability is generally greater than that in inbred strains of animals exposed in controlled experimental conditions.

Working lifetime exposure concentrations

Once the critical dose in human lungs is estimated from the animal data (e.g., associated with risk to a chronic adverse effect), the equivalent workplace airborne concentration over a full working lifetime in humans is derived. This may be accomplished using human lung dosimetry models that account for various physiological characteristics, such as breaths per minute and total volume. The Multiple-Path Particle Deposition Model (MPPD) (CIIT and RIVM 2002) and the International Commission on Radiation Protection (ICRP 1994) models are often used to estimate deposition and clearance of inhaled spherical particles in the human respiratory tract. Additional model evaluation and development may be needed for airborne nanoparticles, such as CNT, which can become airborne in the work environment in various shapes (irregular to fibrous), sizes (nanometer diameters to micrometer lengths), and structures (single or agglomerated).

Determination of an OEL

In the US, the determination of an OEL involves consideration of both the risk-based exposure estimates (typically an 8-hour time-weighted concentration) and sometimes the practicality or technical feasibility of measuring and controlling exposures at or below that concentration. As with other occupational hazards, recommending an OEL for a specific nanomaterial may be contingent on having adequate health effect information, an appropriate sampling and analytical method, and the ability to control exposures at the OEL. Currently, workplace exposure measurements for aerosols in the U.S. are typically based on a mass concentration. If dose metrics different than mass (e.g., particle surface area or

number) are used to predict the risk of exposure to nanoparticles, it will be necessary to make conversions or develop sampling instruments based on these metrics.

Strategies for developing OELs for nanomaterials

Developing OELs is dependent primarily on the available toxicity information (Fig. 2). As with all potential occupational hazards, the assessment of risk of nanomaterials requires relevant hazard and exposure information that can be used in developing an OEL. When there are adequate toxicity data, the approach shown in Fig. 2 is often used for the development of OELs in the U.S. This involves conducting QRAs of published data sets and extrapolating to working periods such as, 8 h/day, 40-h-work-weeks, for a 45-year working lifetime. When there is suggestive or inadequate toxicity data, other approaches for control guidance such as development of “in-house” OELs, control banding or performance-based exposure control limits have been developed (McHattie et al. 1988; Naumann et al. 1996; Paik et al. 2008). Nanomaterials, however, represent additional challenges. Engineered nanoparticles can have varying chemical and physical characteristics and may be structurally and compositionally homogeneous or heterogeneous or even be multi-functional.

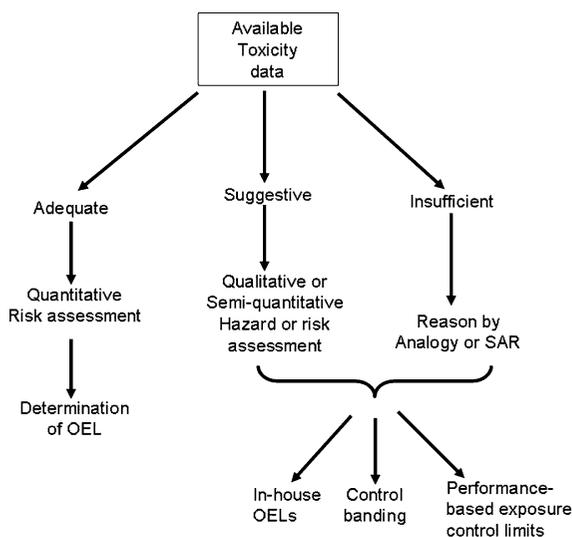


Fig. 2 Approaches to developing OELs and other control guidance

As the size of the particle is made smaller, a greater fraction of the atoms are at the surface, which can affect the surface reactivity and toxicological properties of the particle. At the same time, nanoparticles have a tendency to agglomerate and form larger structures, which influences the amount of time they remain airborne and their inhalability (NIOSH 2009a, b). While it seems likely that particle size and shape will affect the deposition and fate of particles in the human body, few data about what effects these physical characteristics have on causing an adverse effect are available for engineered nanoparticles. However, information is available from the scientific literature on the role of particle size and shape on the deposition of particles and fibers in the human respiratory tract, including what effect their physical and chemical properties have on toxicity (Maynard and Kuempel 2005; Drew et al. 2009).

Currently, there are very few workplace measurements of engineered nanoparticle exposures. Exposure assessment studies that have been conducted are frequently constrained by the absence of having a defined exposure metric (e.g., mass, particle number concentration, surface area) to measure exposures that correlates with evidence of a toxic effect. Interpretation of workplace exposure measurements are further compounded by the presence of incidental nanoparticles from sources within the workplace (e.g., diesel exhaust, combustion products, electrical motors, photocopiers) and from the outdoor environment. Since incidental nanoparticles can exist in a variety of shapes, sizes, and compositions, their airborne presence often interferes with the quantitative assessment of workers' exposures to engineered nanoparticles. The lack of an understanding of the toxicity mechanisms associated with specific engineered nanoparticles confounds the ability to identify a specific exposure metric (particle dimension, size, and surface area) that can be used to assess the potential hazard to workers. Nonetheless, there are data sets for some types of nanomaterials that can allow for the development of OELs. Two examples are for titanium dioxide and CNTs.

Titanium dioxide

Some studies in rats have shown that both fine and ultrafine titanium dioxide appear to be carcinogenic in rats by inhalation with ultrafine considerably more

potent (Lee et al. 1985; Heinrich et al. 1995). These chronic bioassay data have been used in QRA and in development of OELs for fine and ultrafine (nanoscale) titanium dioxide (NIOSH 2005; Dankovic et al. 2007). The risk assessment method involved estimating the particle surface area dose in the lungs associated with a 1/1000 excess risk of rat lung tumors, and extrapolating that dose to humans by adjusting for species differences in lung surface area. Human lung dosimetry models were used to estimate the working lifetime exposure concentration associated with the particle dose in the lungs. The model selection can influence the risk estimates, as shown for titanium dioxide. The estimates of working lifetime mean concentration of *fine* titanium dioxide (100 nm–10 μ m particle size) associated with 95% LCL on the 1/1000 excess risk of lung cancer was 0.3–4.4 mg/m³, depending on the model used to fit the rat lung tumor data. For *ultrafine* titanium dioxide (<100-nm primary particle size), the 95% LCL working lifetime mean concentration associated with a 1/1000 excess risk of lung cancer was 0.04–0.54 mg/m³, depending on the model (NIOSH 2005).

Although various dose–response models adequately fit the rat data and could conceivably be used to develop recommendations for occupational exposures to titanium dioxide, the use of a model averaging procedure incorporates both statistical variability and model uncertainty into confidence limit estimation (Wheeler and Bailer 2007). Model averaging uses all the information from the various dose–response models, weighting each model by how well it fits the data, and constructing an average dose–response model. Wheeler and Bailer (2007) demonstrated via simulation studies that the model averaging method has superior statistical properties to a strategy of simply picking the best-fitting model from the BMD suite. The model average estimate of the working lifetime mean concentration of fine titanium dioxide associated with a 1/1000 excess risk of lung cancer is 9.0 mg/m³, with a 95% LCL of 1.6 mg/m³. The corresponding estimate for ultrafine (including engineered) titanium dioxide is 1.10 mg/m³, with a 95% LCL of 0.19 mg/m³. The National Institute for Occupational Safety and Health (NIOSH) utilizes the 95% LCL estimates as the basis for RELs, as opposed to the MLE, to allow for model uncertainty in the estimates (NIOSH 2005). Some uncertainty exists in whether the underlying risk assessment and resulting

OEL is generalizable for both rutile and anatase titanium dioxide due to differences in their crystalline structure. However, the rat chronic inhalation exposure and lung tumor data used to develop the RELs included both rutile and anatase titanium dioxide (fine and ultrafine particle sizes, respectively), and these data were adequately described by the same dose–response curve using a particle surface area dose metric.

There may be value in considering titanium dioxide to be representative of a whole class of PSLT dusts. The risk for inflammation and cancer for titanium dioxide and other PSLT dusts is related to particle size and surface area (NIOSH 2005; Dankovic et al. 2007). Thus, the draft OEL for ultrafine titanium dioxide developed by NIOSH (2005) could be used as the upper bounds of exposure for engineered nanoparticles that meet the definition of PSLT particles. Clearly, some particles with potent toxicity (e.g., crystalline silica) may also exhibit a greater degree of risk at the nanoscale, and OELs for titanium dioxide (and other PSLT) may not be protective for such engineered nanoparticles. Therefore, OELs for nanoscale forms of other hazard classes of particles would need to be developed.

Carbon Nanotubes

CNTs, specifically single-walled CNTs (SWCNT) and multi-walled CNTs (MWCNT), are of special concern regarding their hazard potential because they are fibrous with high length to diameter ratios (i.e., high aspect ratios nanoparticles (HARNs)). Their nanometer diameters, micrometer lengths, and lung biopersistence evoke concerns about their similarity to asbestos (Poland et al. 2008; Takagi et al. 2008; Drew et al. 2009). Preliminary results from animal studies support the notion that CNTs may act like asbestos when deposited in the lung. Results from animal studies have shown adverse lung effects at relatively low mass doses of CNT, including acute pulmonary inflammation and early onset pulmonary fibrosis without persistent inflammation (Shvedova et al. 2005, 2008; Porter et al. 2009). There is also evidence indicating that some types of well-dispersed MWCNT can move through the outer wall of the lung to the intrapleural space following exposure by pharyngeal aspiration (Hubbs et al. 2009; Porter et al. 2009) and can reach the subpleura and initiate

fibrosis following inhalation exposure (Ryman-Rasmussen et al. 2009). When MWCNT were administered intraperitoneally to mice, asbestos-like pathogenicity was observed (Takagi et al. 2008), especially with the longer (>20 μm) but not the shorter or tangled CNT structures (Poland et al. 2008). In vitro studies have also shown genotoxic effects for some CNTs (Kisin et al. 2007; Zhu et al. 2007; Karlsson et al. 2008; Muller et al. 2008b; Sargent et al. 2009). Although structural defects on the MWCNTs influenced acute pulmonary toxicity (Muller et al. 2008a), it was not a factor in the chronic response (Muller et al. 2009). Rats receiving a single intraperitoneal injection of short MWCNT (<1 μm in length), either with or without structural defects, did not develop persistent inflammation or mesothelioma after 2 years (Muller et al. 2009). It is not known to what extent various types of nanoparticles with high aspect ratios and micrometer lengths could behave like asbestos, although the movement of MWCNTs from the lungs to the subpleura and the pathogenic responses associated with the longer MWCNT structures is consistent with the current paradigm of fiber pathogenicity (Oberdörster et al. 2007; Poland et al. 2008; Ryman-Rasmussen et al. 2009). The risk for developing lung cancer and/or mesothelioma based on size, dimension (length and diameter), and biopersistence of nanoparticles is unknown. However, evidence of mesothelioma from studies with respirable-sized erionite fibers and silicon carbide whiskers indicate that other physiochemical properties (e.g., surface structure or reactivity) may play an important role in toxicity over and above what would be expected for long biopersistent fibers (Merchant 1990; Johnson et al. 1992; Selcuk et al. 1992; Akiyama et al. 2007; Shvedova et al. 2009).

An approach that could be used to derive an OEL for CNT is similar to that discussed earlier for titanium dioxide. This approach involves extrapolating from animals to humans by calculating the mass dose per surface area of lung (dose–response), determining the BMD and equivalent tissue doses, and calculating a working lifetime exposure concentration. An assessment of risk would also need to adjust for the subchronic exposures in rodents to SWCNTs and MWCNTs purified and non-purified. Since these toxicology studies all use mass dose, any derived OEL would likely be expressed as a mass concentration in air. Validated methods for

measuring the airborne concentration of CNTs in the workplace have not been developed; although, elemental carbon measurement using NIOSH Method 5040 (NIOSH 1994) is being used by NIOSH and others in conjunction with transmission electron microscopy (TEM) to verify the presence of CNT in the samples.

To illustrate some of the issues in developing OELs for CNTs, the following example is provided. Using the data from Ma-Hock et al. 2009, which involved Wistar rats exposed at 0.1, 0.5, and 2.5 mg/m³ (6 h/day, 5 days/week for 13 weeks), and following the approach shown in Fig. 1, it is likely that an OEL for a risk of pulmonary fibrosis of less than 1 in 1,000 over a working lifetime would be less than the limit of quantitation of the NIOSH analytical Method 5040 which is 7 µg/m³ for an 8-h TWA. The risk management implications of the computed exposure level in combination with the inability to measure the presence of CNTs below that level could require the use of closed systems or placing workers in full body protection. Such an approach may not be practical for some operations.

Mass/volume may not be the best metric for evaluating airborne concentrations of CNT based on results from some short-term animal studies which implicate the role of fiber dimension and biopersistence in causing toxicological response. Although results from animal studies of CNT do not provide specific information on the relationship between fiber dimension and response, it appears exposure to CNTs can elicit responses that are similar to asbestos fibers (Poland et al. 2008; Takagi et al. 2008; Drew et al. 2009; Jaurand et al. 2009; Seaton et al. 2009). Therefore, it may be useful to evaluate workplace exposures using exposure assessment methods similar to that used for asbestos exposures (e.g. NIOSH Method 7402; ISO 10312). Although data are lacking to perform quantitative analyses of risk based on CNT dimension and number, utilizing the OEL for asbestos of 0.1 f/cm³ may be a reasonable approach in the interim for assessing the effectiveness of exposure controls. However, use of the OEL for asbestos will likely require the use of electron microscopy for analysis since the method used for measuring asbestos (i.e., phase contrast microscopy) cannot detect fibers less than ~250 nm in diameter. This means that individual or agglomerated SWCNT and MWCNT smaller than ~250 nm in diameter

would not be detected. Given the propensity for CNTs to agglomerate and exist as airborne clusters or clumps, the criteria used for counting and sizing would have to account for a variety of structures of different dimensions. ISO Method 10312 has been used to evaluate a range of structures for asbestos exposure assessments and may have utility in evaluating CNT exposures by electron microscopy. The method would need to be incorporated in toxicology studies as a dose metric to provide for a complete hazard evaluation and risk management process.

OELs may be needed for all commercially viable forms of CNTs and carbon nanofibers (CNFs). However, the range of toxicity that might exist for the different forms of CNT, including the various metal catalysts, has not been determined. Chronic dose–response data of both non-cancer and cancer endpoints are needed to better understand the working lifetime risks. However, the current toxicology data could be used to develop initial risk estimates and benchmark OELs for use in evaluating the effectiveness of engineering controls and to trigger use of PPE and the need for medical surveillance. Initial risk estimates and OELs may also be useful in evaluating the adequacy of the sensitivity and the specificity of currently available sampling and analytical methods.

In-house OELs

Early in the development of a new chemical entity, it is not uncommon to have incomplete toxicity data. In these instances, it has been common practice to rely on a combination of internal (in-house) and external data derived from the literature. Once the data have been collected, a toxicological evaluation can be conducted to determine appropriate health endpoints and doses. NOEL and NOAEL data are evaluated to determine a representative dose for a material. Once the dose has been determined, an internal (in-house) OEL might be calculated using the method described by Sargent and Kirk (1988). Using this approach requires the generation or discovery of toxicity data for the chemical of interest. In many instances, the toxicity data are incomplete or may not exist during the development of the OEL. Developing exposure control limits in the absence of a complete data set for QRA is not novel (Naumann et al. 1996). It has been widely practiced in the pharmaceutical industry

(ABPI 1995; Naumann et al. 1996; McHattie et al. 1988). Such efforts often require collaboration among experts in the area of risk assessment and toxicology and experts familiar with the substance and the work environments in which exposures occur. One possible approach is the concept of developing a method for deriving initial estimates of OELs for engineered nanoparticles by adjusting exposure limits that exist for bulk forms of the same chemical (Kuempel et al. 2007). A simplified and somewhat more qualitative version of this approach was used in a BSI document to produce Benchmark Exposure Limits (BSI 2007) (discussed later) for specific engineered nanoparticles.

Control banding

Control banding involves grouping nanomaterials according to their hazard potential and developing exposure limit ranges or bands (Hansen et al. 2007; Maynard 2007; Schulte et al. 2008; NIOSH 2009a, b; Zalk et al. 2009). Such hazard and exposure groupings could facilitate the further development of techniques utilizing banding to assess and stratify risks to select appropriate risk control techniques for exposure to nanomaterials. However, the utility of such an approach is frequently limited by the availability of adequate toxicological data for use in hazard assessment; the absence of such data makes workplace risk characterization and the subsequent selection of appropriate control measures problematic. Another suggested approach is the utilization of categories of nanomaterials based on a variety of factors, including surface chemistry and area, particle shape, particle diameter, solubility, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity, and toxicity of parent material (Paik et al. 2008). This approach utilizes the grouping of similar nanomaterials according to their assessed health hazard and exposures and then matching an appropriate control technology (such as general ventilation, local exhaust, or containment) to it. For each nanomaterial group, exposures are controlled to a defined range or band (such as 0.1–1 mg/m³) (Paik et al. 2008; Schulte et al. 2008; Jackson et al. 2009; Zalk et al. 2009). This approach has the potential to offer the greatest utility to nanomaterial producers and users because it would create hazard bands for nanomaterials based on a set of characteristics, and it would then correlate those hazards to control levels (bands).

Performance-based approaches

An alternative approach similar to “control banding” is a performance-based approach to controlling exposures that focuses on emission mitigation (Naumann et al. 1996). This approach also involves linking hazard categories to control strategies. Air monitoring and wipe test data are used to evaluate the effectiveness of performance-based controls and to detect breaches in a previously validated containment system. Table 1 shows the historical performance of various engineering control options for materials used in the pharmaceutical industry. Those control options may be appropriate for nanomaterials. The level of monitoring depends on the hazard PB-ECL category. However, the ability to establish an effective PB-ECL for engineered nanoparticles is contingent on having adequate toxicological data on the nanomaterial of interest and currently available exposure measurement techniques. Measurement limitations become clear if one considers how a mass concentration of 0.1 mg/m³ translates into particle number concentration (metrics most frequently used to characterize emissions of nanoparticles in the workplace) for 14 manufactured nanomaterials undergoing testing under an OECD sponsorship program (OECD 2008). It has been shown that a concentration of 1,236 gold particles/cm³ (200 nm in size) of air would result in a mass concentration of 0.1 mg/m³ (IFA 2009). The application of 20,000 particles/cm³, as suggested in BSI PD6699-2 (BSI 2007) for these particles, would result in a mass concentration of approximately 1.6 mg/m³. This concentration is similar to the existing exposure limit for respirable dust in some countries (3 mg/m³, BAuA 2009) and below the permissible exposure limit for particles not

Table 1 Historic performance levels of engineering control options for airborne dusts in the pharmaceutical industry

Control technology	Historical performance (µg/m ³)
Open handling with engineered local exhaust ventilation (LEV)	<1,000
Directional laminar flow with (LEV) and vacuum conveyance	10–1,000
Closed systems	1–10
High-containment	<1

Naumann et al. (1996) and Eherts (2004)

otherwise regulated in the U.S. (5 mg/m^3) (OSHA). On the other hand, 20,000 gold particles/per cm^3 (20 nm in size) of air correspond to a mass concentration of only 0.0016 mg/m^3 . This would be substantially below existing exposure limits for respirable dust. It was also shown that when the size of nanoparticles and their density vary more than one order of magnitude, the range in particle number concentration exceeds five orders of magnitude (IFA 2009). Particle number concentrations across this wide range cannot be measured by any single current sampling instrument. Therefore, it has been suggested that the size and the density of nanoparticles should also be included in the criteria for developing OELs (IFA 2009).

Overview of global and national efforts to develop OELs for nanomaterials

World-wide efforts at developing OELs for nanomaterials are intensifying. Table 2 lists proposed OELs by various health organizations for certain types of engineered nanomaterials. Global efforts aimed at

developing OELs for engineered nanomaterials were reviewed in an OECD workshop in 2008. At the June, 2009 ISO TC229 meeting, an international group of experts working on the draft Technical Specification “Guide to safe handling and disposal of manufactured nanomaterials” agreed that “(it) will contain guidance for how companies/organizations can make their own decisions regarding benchmark exposure limits, including specific examples for how to develop internal benchmarks as well as citing specific guidelines that can be followed” (ISO 2009).

In addition to the NIOSH proposed exposure limit for nanoscale titanium dioxide, other national efforts to develop OELs for engineered nanomaterials have been reported as being underway in Germany and UK. A German Ministry of Labor and Social Affairs technical rule for hazardous substances in the workplace (TRGS 900) states that the general dust limit value of 3 mg/m^3 for the respirable fraction does not apply to nanoscale particle fraction (BAuA 2009). The German Federal Institute for Occupational Safety and Health (BAuA) published risk-associated exposure levels for respirable biopersistent particles of toner containing a large fraction of nanoscale

Table 2 Proposed OELs for engineered nanoparticles

Nanomaterial	Parameter	OEL	References
General	0.004% risk level	Mass-based OEL: 15	OECD (2008)
Titanium dioxide	0.1 risk level particles < 100 nm	0.1 mg/m^3	NIOSH (2005)
General dust		3 mg/m^3	BAuA (2009)
Photocopier Toner	Tolerable risk	0.6 mg/m^3	BAuA (2008b)
	2009 acceptable risk	0.06 mg/m^3	
	2018 acceptable risk	0.006 mg/m^3	
Biopersistent granular materials (metal oxides, others)	Density > $6,000 \text{ kg/m}^3$	$20,000 \text{ particles/cm}^3$	IFA (2009)
Biopersistent granular materials	Density < $6,000 \text{ kg/m}^3$	$40,000 \text{ particles/cm}^3$	IFA 2009
CNTs	Exposure risk ratio for asbestos	0.01 f/cm^3	IFA (2009)
Nanoscale liquid		Mass-based OEL	IFA (2009)
Fibrous	3:1; length 75,000 nm	0.01 f/cm^3	BSI (2007)
CMAR ^a		Mass-based OEL: 10	BSI (2007)
Insoluble	Not fibrous	Mass-based OEL: 15	BSI (2007)
Soluble	Not fibrous	Mass-based OEL: 10	BSI (2007)
	Not CMAR		
MWCNT	Bayer product only	0.05 mg/m^3	Bayer (2010)
MWCNT	Nanocyl product only	0.0025 mg/m^3	Nanocyl (2009)

^a Carcinogenic, mutagenic, asthmagenic, and reproductive toxicants

particles (BAuA 2008a). Based on a concept of risk developed by the committee for hazardous substances of the German Ministry of Labor and Social Affairs (BAuA 2008b), a tolerable risk (4/1000) is defined as a concentration of 0.6 mg/m^3 , a current acceptable risk (4/10000) is defined as concentration of 0.06 mg/m^3 , and a future acceptable risk (from 2018) is defined as a concentration of 0.006 mg/m^3 .

In light of data paucity on nanomaterial hazard and exposure assessment, the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA 2009) recommended the following benchmark limits to be used for an 8-h work shift and to be used for monitoring the effectiveness of protective measures in the workplace (IFA 2009):

1. For metals, metal oxides and other biopersistent granular nanomaterials with a density of $>6,000 \text{ kg/m}^3$, a particle number concentration of $20,000 \text{ particles/cm}^3$ in the range of measurement between 1 and 100 nm should not be exceeded;
2. For biopersistent granular nanomaterials with a density below $6,000 \text{ kg/m}^3$, a particle number concentration of $40,000 \text{ particles/cm}^3$ in the measured range between 1 and 100 nm should not be exceeded;
3. For CNT for which no such manufacturer's declaration is available, a provisional fiber concentration of 0.01 f/cm^3 should not be exceeded, based upon the exposure risk ratio for asbestos (BAuA 2008c). It is recommended that only CNTs that have been tested for adverse health effects similar to those of asbestos (according to the manufacturer's declaration) to be used;
4. For nanoscale liquid particles (such as fats, hydrocarbons, siloxanes), the applicable maximum workplace limit (MAK) or workplace limit (AGW) values should be employed owing to the absence of effects of solid particles;

These recommended benchmark limits are geared to minimizing the exposure in accordance with the state of the art in measurements. Since these limits are not based on observed health effects, a health risk may still exist for workers, even where these recommended limits are followed. Therefore, benchmark limits should not be confused with health-based OELs (IFA 2009). In the UK, BSI published a public document PD 6699-2 "Guide to safe handling and

disposal of manufactured nanomaterials" (BSI 2007), which provides prescriptive risk guidance for the development, manufacture, and use of nanomaterials. In this document, all nanomaterials are grouped into four hazard categories with assigned Benchmark Exposure Levels (BELs). Similar to the BGIA recommendations, BELs are described as "pragmatic guidance levels only" and are derived from OELs for larger particle forms "on the assumption that the hazard potential of the nanoparticle form is greater than the large particle form." First, there is the "fibrous" category, defined as an insoluble nanomaterial with a high aspect ratio (ratio $> 3:1$ and length $> 5000 \text{ nm}$), which is assigned a BEL of 0.01 f/cm^3 (one tenth of the asbestos OEL prescribed in the U.S. and elsewhere). Second, there is the "CMAR" category, defined as any nanomaterial which is already classified in its larger particle form as a Carcinogenic, Mutagenic, Asthmagenic, or Reproductive toxicant. Nanomaterials in the CMAR category are assigned BELs at one tenth of the mass-based OEL for its larger particle form. Third, there is the "insoluble" category, defined as insoluble or poorly soluble nanomaterials not in the fibrous or CMAR category. Nanoparticles in this category are assigned BELs at one fifteenth of the mass-based OEL for its larger particle form or $20,000 \text{ particles/cm}^3$. Fourth, there is a "soluble" category, defined as a soluble nanomaterial not in fibrous or CMAR category, which is assigned a BEL at one half of the mass-based OEL for its larger particle form.

In addition, it has been recommended that any new OEL for nanomaterials should satisfy the following limiting conditions (IFA 2009):

1. when there is no sufficient information on hazards and exposures of nanomaterial, precautionary principles should apply;
2. existing "general" exposure dust limits and exposure limits for the same compounds in macroscopic form cannot be exceeded;
3. the proposed exposure limits should not be higher than exposure limits achieved with affordable engineering controls;
4. the proposed exposure limits should be measurable with affordable monitoring techniques.

A number of efforts world-wide are underway to conduct studies aimed at obtaining data which could be used in QRA analysis to develop OELs. Perhaps

the largest effort to generate dose–response and other hazard-related data is OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials. Under this program, OECD member countries, as well as some non-member economies and other stakeholders, are working together to evaluate the hazard potential of 14 manufactured nanomaterials, which are in, or close to, commercial applications (OECD 2008). Most recently, Bayer MaterialScience conducted subchronic inhalation studies on MWCNTs and derived in-house an OEL of 0.05 mg/m^3 for its MWCNT product (Bayer 2010). Nanocyl utilizes a no effect concentration in air of 0.0025 mg/m^3 for an 8-h/day exposure (Nanocyl 2009). This limit was estimated from the lowest observed adverse effect level of 0.1 mg/m^3 obtained using data from the 90-day inhalation study following OECD 413 guidelines and by applying an assessment factor of 40 (Ma-Hock et al. 2009; Nanocyl 2009).

Additionally, the European Union regulatory framework REACH (Registration, Evaluation, and Authorisation of Chemicals) specifies using standard regulatory toxicology tests, quantitative structure activity relationships (QSARs), and physiologically based pharmacokinetics models (PBPKs). Using the data from these types of tests, REACH stipulates developing derived no-effect level (DNEL) of exposure and comparing the DNEL with exposure levels from different scenarios in relevant exposure assessments (Seaton et al. 2009).

Future considerations

Given the potentially vast variety of nanomaterials, it would be a considerable challenge to engage in the development of substance-by-substance OELs. However, there may be alternative approaches that could be used to overcome these limitations. A more workable alternative could be to develop health standards, including OELs, for groups of nanomaterials which have similar molecular identity (e.g., CNTs, metal oxides and metals), as the Organization for Economic Co-operation and Development has recommended (OECD 2008). However, the grouping of nanomaterials by similar molecular identity or shape may overlook other physicochemical characteristics (e.g., functionalization, surface reactivity) which can cause dramatic differences in biological activity.

Another general approach would be to develop “categorical” OELs based on a QRA for broad compositional categories, e.g., metal oxides, CNTs, quantum dots, and others using the most sensitive health end point identified within this group of nanomaterials. These benchmark OELs could then apply to the whole compositional category. However, there could be great variability in toxicity within compositional categories. It may be better to utilize categories based on the mode of action (Nel et al. 2006; Schulte et al. 2009). For example, nanoparticles that cause the formation of reactive oxygen species might be grouped together and an OEL developed for that category.

More broadly, a programmatic approach based on a public–private partnership has been suggested for nanomaterials that include generic provisions for exposure assessment, risk controls, medical surveillance, and worker training for protecting the health of workers exposed to engineered nanoparticles (Howard and Murashov 2009). As the quantitative assessment of the nanotechnology risks emerge, the information generated, collected, and utilized by the proposed National Nanotechnology Partnership program (Howard and Murashov 2009) could serve as a “tentative” OEL (McGarity 1992). Subsequently, if sufficient evidence of “significant risk” becomes available for a specific nanomaterial, an occupational health standard could be developed. The proposed National Nanotechnology Partnership program could help overcome the significant time lag between the generation of sufficient risk assessment information and the development of occupational health and safety standards. The regulatory requirements in the U.S. for setting occupational safety and health standards has precluded regulators from taking incremental and precautionary steps toward protective standards on the basis of less-than-complete risk assessment and control information (Howard and Murashov 2009).

Ultimately, a coordinated approach is needed between government, industry, and other social partners that identifies the extent to which specific nanomaterials are and will be used in commerce, and that encourages toxicologic testing, the conduct of qualitative and QRAs, and the voluntary implementation of risk management measures until the need for mandatory risk reduction approaches are identified. The knowledge base about toxicity of nanomaterials

is growing but generally quite limited in understanding how the various compositional characteristics of engineered nanoparticles influence toxicity. Knowledge of the extent to which human exposure occurs in the workplace and in the general population is also limited, making risk characterization difficult. Yet, preliminary evidence has generated sufficient concern among occupational health and safety managers to consider developing risk management programs (Schulte et al. 2008). Performance-based engineering controls, control banding, and interim OELs can be useful steps to minimize the health risks to workers and to serve as a means for assessing the effectiveness of exposure control measures and making other risk management decisions.

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