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Review

Risk Assessment and Risk Management of Nanomaterials in the Workplace: Translating Research to Practice

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In the last decade since the rise in occupational safety and health (OSH) research focusing on nanomaterials, some progress has been made in generating the health effects and exposure data needed to perform risk assessment and develop risk management guidance. Yet, substantial research gaps remain, as do challenges in the translation of these research findings to OSH guidance and workplace practice. Risk assessment is a process that integrates the hazard, exposure, and dose–response data to characterize risk in a population (e.g. workers), in order to provide health information needed for risk management decision-making. Thus, the research priorities for risk assessment are those studies that will reduce the uncertainty in the key factors that influence the estimates. Current knowledge of OSH in nanotechnology includes the following: (i) nanomaterials can be measured using standard measurement methods (respirable mass or number concentration), (ii) workplace exposures to nanomaterials can be reduced using engineering controls and personal protective equipment, and (iii) current toxicity testing and risk assessment methods are applicable to nanomaterials. Yet, to ensure protection of workers' health, research is still needed to develop (i) sensitive and quantitative measures of workers' exposure to nanomaterials, (ii) validation methods for exposure controls, and (iii) standardized criteria to categorize hazard data, including better prediction of chronic effects. This article provides a state-of-the-art overview on translating current hazard research data and risk assessment methods for nanomaterials to the development and implementation of effective risk management guidance.

Keywords: hazard assessment; nanomaterials; occupational exposure; occupational exposure limit; occupational health; respirable dust; risk assessment; risk management

INTRODUCTION

Nanotechnology is a recognized cross-cutting technology that enables applications across all economic sectors [International Organization for Standardization (ISO), 2008; Organization for Economic Cooperation and Development (OECD), 2008]. Yet, the potential adverse health effects remain poorly characterized for many nanomaterials. With the increase in production and use of nanomaterials comes the potential for increased exposure of workers to nanomaterials (Invernizzi, 2011). Guidance on working safely with nanomaterials has been developed in the past decade by government agencies, academia, and occupational health organizations [e.g. The Royal Society, 2004; Maynard and Kuempel, 2005; Oberdorster *et al.*, 2005b; BSI, 2007; ISO, 2009; National Institute for Occupational Safety and Health (NIOSH), 2009a; OECD, 2009; ANSES, 2010; Cornelissen *et al.*, 2011]. However,

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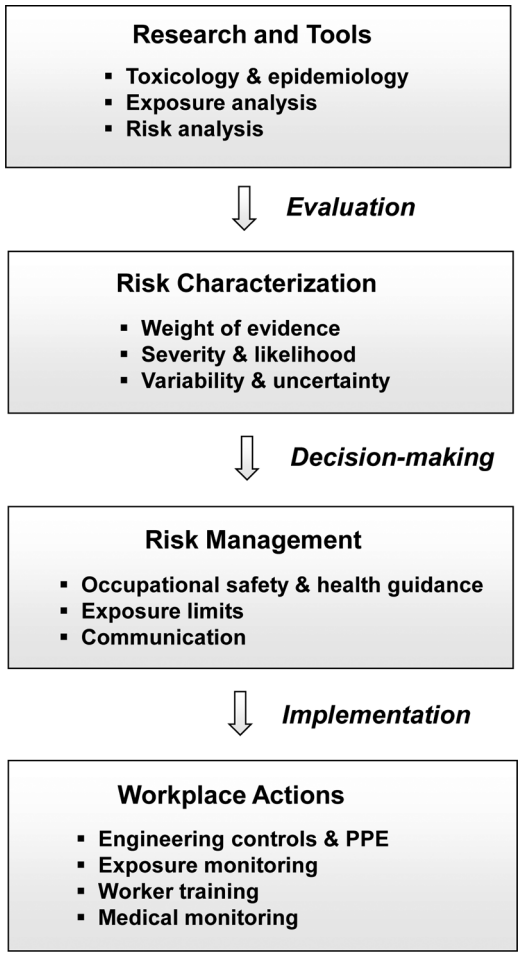

Fig. 1. Components for assessing, characterizing, communicating, and managing risks. (PPE: personal protective equipment).

the extent to which that guidance is followed is not well known, and validation of the effectiveness of the exposure controls and measurement methods for nanomaterials remains a key research need. In the absence of regulatory occupational exposure limits (OELs) for most nanomaterials, a strategy is needed to assess the hazard and determine the appropriate levels of exposure control to protect workers' health.

An effective occupational safety and health (OSH) program for nanomaterials (or hazardous materials generally) integrates the components of basic research, guidance development, and workplace actions (Fig. 1). This integrated scheme can also be viewed as a research-to-practice approach (www.cdc.gov/niosh/r2p/). The current state-of-the-science for nanomaterials with respect to OSH consists of a still-limited but increasing toxicological data base, although there is no standardized framework yet for evaluating and interpreting those data. As such, the translation of research findings to guidance and action has been relatively piecemeal for nanomaterials (as for occupational hazards generally), such that workers may have different levels of health protection depending on the health-effects data available for a specific substance and the extent to which exposure controls are implemented.

This article provides an overview of what we know and what we still need to know concerning OSH research and practices as it relates to nanomaterials. 'We' refers to the OSH community including the NIOSH Nanotechnology Research Center (NTRC) (NIOSH, 2010a,b). Specific examples [e.g. carbon nanotubes (CNT)] of the data needed for risk assessment to support risk management decision-making, focusing on inhalation hazards, are provided. An integrated process is proposed for the evaluation, decision-making, and implementation of OSH research and guidance.

WHAT WE KNOW

Recent evaluations of current methods for exposure measurement and control have generally shown that these are effective in reducing exposure of workers to nanomaterials (Methner, 2008; NIOSH, 2009a). The next step is to evaluate if these exposure controls are sufficiently health protective, which requires linkage to hazard data and risk estimates. In some cases (e.g. CNT), more sensitive sampling and analytical methods may need to be developed (NIOSH, 2010c). Examples of the state-of-the-science and specific research gaps at each stage of a comprehensive OSH process (Fig. 1) are suggested in Tables 1–3.

Nanomaterial OELs

The most important measure to protect workers' health is to minimize (reduce or eliminate) exposures to hazardous substances in the workplace. This is accomplished through effective application of engineering controls and personal protective equipment as part of a risk management program. OELs are intended to guide the control of workplace exposures to levels that would not cause material impairment of health. Relatively few specific OELs have been developed for nanomaterials (reviewed in Schulte *et al.*, 2010; examples in Table 4), and none of these are regulatory standards.

Current proposed nanomaterial OELs are generally low mass concentrations compared with existing OELs for larger respirable particles of the same chemical composition (e.g. metal oxides and

Table 1. Examples of research progress and knowledge gaps in predicting hazard potential of nanomaterials.[a]

What we know	What we still need to know
• Biological responses can depend on particle properties,[b] such as size, shape, surface area, surface chemistry, and solubility	• The difference between the influence of particle properties and other study design differences • Results from assessments with standard materials and response measures
• Some relationships between *in vitro* and 'acute' *in vivo* animal responses have been demonstrated (example: metal oxides and reactive oxygen species associated with inflammation responsec	• How to predict 'chronic' responses in animals and humans • A more complete understanding of the role of physical–chemical properties by mode-of-action category

[a]Examples of physical and biological metrics evaluated in 'Research and tools' in Fig. 1. This list is not comprehensive.
[b]Maynard and Kuempel (2005), Oberdörster *et al.* (2005), OECD (2010b), and Castranova (2011).
[c]Donaldson *et al.* (2010), Rushton *et al.* (2010), and Puzyn *et al.* (2011).

Table 2. Progress and gaps in the information needed to support OSH guidance in nanotechnology workplaces.[a]

Where we are	Where we need to be
• Have made advances in exposure instrumentation and measurement strategies[b]	• Need sensitive, specific, and quantitative measure of workers' exposure
• Have sensitive measures of biological response in experimental systems[c]	• Need framework to interpret hazard data with respect to workers' health risk
• Have partially delineated the role of nanomaterial physical–chemical properties in toxicity[d]	• Need validated predictive models to make risk management decisions
• Have developed good work practices and general guidance documents[e]	• Need to demonstrate effectiveness of exposure controls in specific work processes

[a]Relates to the evaluation and decision-making steps of a comprehensive OSH process (Fig. 1).
[b]ISO (2007), Brouwer *et al.* (2009), NIOSH (2010c), Bau *et al.* (2010), Görner *et al.* (2010), Johnson *et al.* (2010), and Ramachandran *et al.* (2011).
[c]Sargent *et al.* (2011), Castranova (2011), and Mercer *et al.* (2011).
[d]Duffin *et al.* (2007), Sager and Castranova (2009), Wang *et al.* (2010), and Pauluhn (2011).
[e]BSI (2007), NIOSH (2009a), ISO (2009), OECD (2009), and ANSES (2010).

Table 3. Closing the implementation gap—strategic actions in translating the state-of-the-science to protect nanotechnology workers' health.[a]

What we need to do	How we can get there
• Enhance risk communication tools	• Develop focused strategies on best practices in exposure control in laboratories, scale-up, and production workplaces
• Emphasize containment and control	• Utilize hazard and control banding tools as a first step and validate effectiveness
• Compare toxicity to existing substances	• Use standardized assays to compare nanoparticle properties and bioactivity with benchmark particles, also look for new effects and/or target organs
• Implement hazard- and risk-based management of nanomaterials	• Develop criteria for nanomaterial hazard categories, occupational exposure controls, and safe and responsible uses of nanomaterials

[a]Examples for implementing risk management guidance to develop effective workplace solutions (final step in a comprehensive OSH process) (Fig. 1).

carbonaceous particles) (Table 4). Among the proposed nanomaterial OELs, the differences among the same or similar materials may be largely due to different methods and assumptions used to derive the OELs (Table 4) (discussed further below). Despite these differences, there is relative consistency in the OELs within particle types, and these generally fall within the same exposure control bins (e.g. order-of-magnitude categories) (Hewett *et al.*, 2006). Each of these bins is associated with specific engineering control options, based on proven control technologies from other industries (e.g. pharmaceuticals, cosmetics, and dry powder processes) (Naumann *et al.*, 1996). The CNT OEL estimates fall within either 1–10 or 10–100 μg m^{-3} [8-h time-weighted average (TWA)], which may be achievable

Table 4. Examples of proposed OELs for nanomaterials and the associated exposure control bin.

Substance	OEL (μg m^{-3})[a]	Basis	References	Exposure control bin (μg m^{-3})
TiO_2—ultrafine	610[b]	Estimated human-equivalent concentration to rat subchronic estimated NOAEL[c] of 2 mg m^{-3} (Bermudez *et al.*, 2004), UF of 3	Gamo (2011), Nakanishi (2011a)	100–1,000
TiO_2—ultrafine	300	Working lifetime (45-year) excess risk <1/1,000 (95% LCL estimate) based on benchmark dose model average estimate of particle surface area dose and rat lung tumor response. MOA: secondary genotoxicity from persistent pulmonary inflammation	NIOSH (2011)	
Fullerene (C_{60})	390[b]	Estimated human-equivalent concentration to rat NOAEL of 0.12 mg m^{-3} (from 28-day inhalation, estimated subchronic equivalent), UF of 9	Shinohara (2011), Nakanishi (2011a)	
MWCNT	50	Estimated human-equivalent rat NOAEL of 0.1 mg m^{-3} (Pauluhn, 2010a) by breathing rate, exposure time, deposition, alveolar macrophage volume, and retention kinetics; no UF	Pauluhn (2010b)	10–100
CNT	30[b]	Estimated human-equivalent concentration to rat 28-day NOAEL of 0.13 mg m^{-3} for SWCNT and 0.37 for MWCNT. Proposed the lower SWCNT value for all CNT[d], UF of 6	Nakanishi (2011a,b)	
CNT and CNF	7 (draft)	Set at LOQ of measurement method. Working lifetime (45 year) excess risk >10% (95% LCL estimate) of early-stage pulmonary inflammation or fibrosis in rat or mouse short-term or subchronic studies	NIOSH (2010c)	1–10
MWCNT	1-2	Adjusted rat NOAEL or LOAEL of 0.1 mg m^{-3} (Pauluhn, 2010a; Ma-Hock *et al.*, 2009, respectively) for exposure day and breathing rate, UF of 25 or 50	Aschberger *et al.* (2010)	

Abbreviations: TiO_2, titanium dioxide; MOA, mode of action; UF, uncertainty factor.
[a]8-h TWA concentration.
[b]OEL (PL): 15-year period-limited OEL. Rat to human adjustments: breathing rate, exposure time, deposition, and body weight.
[c]Bermudez *et al.* (2004) report responses in rat at 2 mg m^{-3}, suggesting that it could be interpreted as a LOAEL.
[d]An OEL (PL) of 0.08 mg m^{-3} was also derived for a MWCNT (44-nm diameter); however, the OEL (PL) of 0.03 mg m^{-3} for a SWCNT with the largest specific surface area was proposed as the common value for CNT.

with containment systems or ventilated enclosures, respectively (Naumann *et al.*, 1996; Ader *et al.*, 2005; Zalk and Nelson, 2008).

The applicability of existing OELs for larger particles to those with nanoscale forms has generally not been evaluated (except, for example, NIOSH, 2011). Moreover, the health basis for existing OELs can vary based on the type of data and methods used to derive the OEL, whether a quantitative risk assessment (QRA) was performed, and the extent to which technical or economic feasibility was given consideration. Thus, standardized risk assessment methods [National Research Council (NRC), 2009; OECD, 2010a] are needed to provide a more consistent health-based approach for setting OELs for nanomaterials.

Risk Assessment: Basic Principles

Occupational health risk assessment is a process to evaluate the hazard, exposure, and dose–response data to characterize risk in workers. Risk estimates provide information to support the development of OELs and other risk management measures. The basic steps in a comprehensive risk assessment (NRC, 2009) include the following:

(i) Problem formulation;
(ii) Risk assessment;
    a. Hazard assessment;
    b. Exposure assessment;
    c. Dose–response assessment;
    d. Risk characterization;
(iii) Risk management and risk communication.

Problem formulation is an initial evaluation of the nature of the hazard, the options for exposure control, and the data needed to distinguish among those options. This step makes risk assessment more efficient by identifying at the beginning of the process

the information of most value that will be needed for decision-making. Hazard assessment is an evaluation of the nature and severity of biological effects (typically in toxicology studies). Exposure assessment involves the measurement or estimation of workers' exposures, by task or full shift. Dose–response assessment (e.g. in animal studies) provides information on the measured or model-estimated dose and the biological responses that are considered relevant to human health. A critical effect level is estimated from the dose–response data (e.g. BMDL, LOAEL, or NOAEL). BMDL is the 95% lower confidence limit estimate on the benchmark dose (maximum likelihood estimate), estimated from statistical modeling of the dose–response data. LOAEL is the lowest observed adverse effect level, and NOAEL is the no observed adverse effect level (i.e. the highest dose that is not statistically significantly associated with exposure-attributable adverse effects). The animal critical effect is extrapolated to humans by normalizing the dose across species (e.g. per unit of target tissue) and by adjusting for the dose rate (e.g. assuming 'Haber's principle' that cumulative exposure, i.e. concentration × time, would result in equivalent responses).

QRA is the estimation of the severity and likelihood of an adverse response associated with exposure to a hazardous agent (NRC, 2009). QRA involves not only the best estimate (i.e. central tendency) but also the variability in that estimate, given the data, and the uncertainty in the models and methods used to derive those estimates. Variability is a measure of the distribution of a parameter in a population and can be characterized with measurement data. Uncertainty is the degree of ambiguity, such as in the nature of the hazard or the model used to describe the dose–response relationship. Risk characterization brings together the findings from hazard, exposure, and dose–response assessments to provide information to support the risk management decision-making and risk communication. In the absence of complete risk characterization, or given large uncertainties, additional precaution in the exposure control may be needed to ensure that workers are adequately protected (Schulte and Salamanca-Buentello, 2007).

PROGRESS IN KEY AREAS

Hazard assessment: considerations on nanomaterials

Hazard assessment, in concept, is the same for nanomaterials as for other substances. Current toxicology tests and assays are considered generally applicable to hazard evaluation of nanomaterials (Oberdörster *et al.*, 2005a; OECD, 2008, 2010b). Yet, there may be substance-specific factors that need to be considered in evaluating toxicity, including those for nanomaterials. Some factors that may influence the toxicity of nanomaterials relative to larger particles of the same chemical composition include the following:

- Dose metric;
- Target tissue;
- Physical–chemical properties.

These interrelated factors can affect the uptake and interaction of nanomaterials with biological systems and thus may influence the internal dose and response.

Dose metric. The mass dose metric (exposure concentration in air or lung dose) has been shown to be a poor predictor of toxicity for poorly soluble nanoparticles compared with larger respirable particles (e.g. carbonaceous; metal oxide). Particle surface area dose (Oberdörster *et al.*, 1994; Tran *et al.*, 2000; Bermudez *et al.*, 2002, 2004; Elder *et al.*, 2005; Duffin *et al.*, 2007; NIOSH, 2011) and particle volume (Morrow, 1988; Pauluhn, 2011) have been shown to better predict the lung responses in rats or mice across a range of particle sizes. Agglomeration can influence the deposited dose since the airborne particle size determines the deposition efficiency in the respiratory tract. The form of the nanomaterial to which workers may be exposed should be tested, including if the form is altered by downstream users of the nanomaterial or nanomaterial-containing product, to best estimate the risk of occupational exposure.

Target tissue. The respiratory tract, and specifically the alveolar (gas-exchange) region, is the main target for the deposited dose of respirable particles including nanoparticles. The deposition efficiency of inhaled particles generally increases with decrease in particle size into the nanoscale range [International Commission on Radiological Protection (ICRP), 1994; Maynard and Kuempel, 2005]. Adverse respiratory effects have been reported in workers (exposed to airborne particles or fibers) and in the general population (from exposure to particulate air pollution) (Pope *et al.*, 2002; Rom and Markowitz, 2006). Some types of nanoparticles have been shown to escape normal lung clearance processes (alveolar macrophage phagocytosis) (Renwick *et al.*, 2001) and enter the lung interstitium to a greater extent (Mercer *et al.*, 2010, 2011). Of the nanoparticles studied thus far, the proportion of the mass dose that translocates from the lungs to other organs has been

found to be low (Kreying *et al.*, 2002). Yet, nanoparticles may gain access to cells and cell organelles that are not readily accessible to larger particles, and individual nanoparticles have been seen in the cell nucleus, interacting with DNA (Geiser *et al.*, 2005; Sargent *et al.*, 2011b). Ultrafine (nanoscale) particles have also been observed in the mitochondria of treated cells (murine macrophages and human bronchial epithelial cell lines) to a greater extent than fine-size particles; nanoparticles generated more reactive oxygen species per unit mass, causing structural damage (Li *et al.*, 2003). Possible effects outside of the lungs also need to be evaluated, since nanoparticles have been shown to translocate (migrate) from the lungs to the systemic circulation and to other organs in rats and mice (Semmler *et al.*, 2004; Geiser and Kreyling, 2010), as well as from the nasal region via olfactory nerves to the brain in rats (Oberdörster *et al.*, 2004; Elder *et al.*, 2006). These routes have not been demonstrated conclusively in humans, but similar biological structures and mechanisms suggest that these pathways could occur as in animals (Oberdörster *et al.*, 2005b).

Physical–chemical properties. Particle size, shape, surface area, surface reactivity, solubility, and functionalization can all influence the particle toxicity (Oberdörster *et al.*, 2005b; Castranova, 2011). These properties can influence the internal dose and toxicity at the initial target tissue and distal organs. The toxicity may be either increased or decreased for soluble particles, depending on the biological mode of action (Castranova, 2011; Cho *et al.*, 2012). Because of the greater surface area per unit mass, nanoparticles may be more soluble than larger particles. The degree of agglomeration may also influence the dissolution rate. Some progress has been made toward developing predictive models based on the properties of nanoparticles (e.g. Rushton *et al.*, 2010; Puzyn *et al.*, 2011). These models of quantitative structure–activity relationships (QSAR) require standardized data obtained in controlled experiments in order to evaluate the influence of the specific nanoparticle properties on the dose–response relationships. In the absence of such models, a more time-consuming case-by-case assessment of risk may be necessary. A categorical approach to OEL development (discussed further below) based on the physical–chemical properties could be very useful, in the absence of specific OEL guidance, to make exposure control decisions.

Risk assessment methods for nanomaterials

The current risk assessment process (NRC, 2009) is generally considered to be applicable to nanomaterials. Although the risk assessment process for nanomaterials is not unique, there are aspects that pertain to risk analyses of sparse or incomplete data. For example, when data are limited, there may be insufficient information to distinguish between alternative plausible models, resulting in large differences (e.g. >10×) in the quantitative estimates (NIOSH, 2010c). In such cases, estimating an OEL band may be an initial step until more precise data can be obtained to develop a more specific OEL.

Recent risk evaluations of nanomaterials (e.g. CNT) have focused on adjustments of the NOAEL or LOAEL from animal short-term or subchronic studies, using various interspecies scaling factors and/or uncertainty factors (Table 4). Differences in methods and assumptions can result in different OELs, even based on the same animal data. Starting from the NOAEL from a subchronic inhalation study of one type of multiwall CNT (MWCNT) (Pauluhn, 2010a), Pauluhn (2010b) estimated an OEL of 50 μg m^{-3} by applying a total interspecies adjustment factor of 2 and no uncertainty factors. Aschberger *et al.* (2010) estimated an OEL of 2 μg m^{-3} based on the same NOAEL but using different interspecies dose scaling and uncertainty factors. Starting from the NOAEL in a 28-day rat intratracheal instillation study of another type of MWCNT, Nakanishi (2011a) derived an OEL of 30 μg m^{-3} as a period-limited (15-year) OEL. None of these assessments fully accounted for the differences in rat and human long-term lung clearance kinetics of inhaled particles generally or for the uncertainty in these estimates for nanoparticles. In a QRA of various types of CNT, NIOSH (2010c) estimated >10% excess risk (95% upper confidence limit estimates) of early-stage lung effects (inflammation, alveolar–interstitial thickening, or fibrosis) over a 45-year working lifetime at 7 μg m^{-3} (8-h TWA), which is the upper limit of quantification (LOQ) for the NIOSH sampling and analytical method for elemental carbon (NIOSH, 2010c). NIOSH set the draft REL at the LOQ and recommended the development of more sensitive measurement methods as a priority research area.

Risk assessment steps. Four standard factors are used to adjust an animal NOAEL (or other effect level) to estimate a human-equivalent dose of inhaled particles (Kuempel *et al.*, 2006):

(i) Ventilation per exposure day (H/A);
(ii) Deposition fraction (H/A);
(iii) Dose retention kinetics (H/A);
(iv) Interspecies dose normalization (A/H),

where the species-specific factor is for humans (H) or animals (A). These factors are multiplied to

obtain the total adjustment factor, which is divided into the animal NOAEL to obtain the estimated human-equivalent NOAEL [e.g. Pauluhn (2010b) or Environmental Protection Agency (EPA) (1994) and similar approaches].

Example of CNT

Quantitative uncertainty. Ventilation and deposition (factors 1 and 2) can be estimated with relatively low uncertainty based on existing measured values in humans and animals and on prediction models for spherical particles that provide estimates of deposition efficiency within the respiratory tract region by airborne particle size, e.g. multiple-path particle dosimetry (MPPD) [CIIT and RIVM, 2006; Applied Research Associates (ARA), 2011]. In contrast, retention kinetics and dose normalization (factors 3 and 4) can have a large influence on the risk estimates due to the relatively limited data available to evaluate alternative models and assumptions in the estimation of the human-equivalent lung dose. Lack of adjustment for interspecies differences in lung clearance kinetics (factor 3) has the same effect as assuming simple steady-state kinetics at the same rate in both species. This is clearly incorrect based on available data of particle clearance in animals and humans, e.g. Snipes (1989) estimated a 10× slower long-term clearance rate in humans than in rats. Moreover, the ICRP (1994) clearance model-based estimates of the human-equivalent chronic lung burdens (45-year working lifetime) are a factor of ~30× greater than the estimated equivalent rat lung burden after chronic (2-year) exposure [estimated at 0.1 mg m^{-3}, NOAEL in Pauluhn (2010a), in MPPD rat and human models (CIIT and RIVM, 2006; NIOSH, 2010c; ARA, 2011)]. A recent human respiratory tract model update would increase the average human-retained lung dose estimates by another factor of 2–3 (Gregoratto *et al.*, 2010, 2011). Thus, assumptions about dose rate and clearance kinetics can have a substantial influence (~10–100×) on the estimate of the human-equivalent lung dose of poorly soluble particles, and therefore on the OEL estimate.

Differences in the interspecies dose normalization assumptions (factor 4) can also have a moderately large influence on the human-equivalent dose estimates. For example, normalizing the dose by the average alveolar epithelial surface area (0.4 m^2/102 m^2) (rat/human) (Mercer *et al.,* 1994) versus by the total alveolar macrophage cell volume (3.0×10^{10} μm^3/3.5×10^{13} μm^3) (rat/human) (Pauluhn, 2010b) results in a ~4.5× difference in the human-equivalent dose estimate.

Given the uncertainty in the CNT lung dose estimates in workers, the NIOSH risk assessment evaluated the bounds of the estimated lung doses, by assuming either normal clearance or no clearance of the deposited dose predicted from spherical particle models (CIIT and RIVM, 2006; NIOSH, 2010c). Some evidence suggests that the true lung dose estimate may lie within these bounds, i.e. CNT particle clearance was observed to be slower than expected for other respirable poorly soluble particles at low airborne mass concentrations (Pauluhn, 2010a). Risk estimate differences due to lung dose assumptions were greater (~4–5×) than those due to the interstudy differences (~2×) (Table 5). The OELs are all based on short-term or subchronic data, and none explicitly address possible carcinogenic end points (Table 4).

Qualitative uncertainty. The structural similarities of CNT that resemble asbestos have lead to concerns about asbestos-type pathology (Takagi *et al.*, 2008; Jaurand *et al.*, 2009; Donaldson *et al.*, 2010). In addition to the noncancer lung effects (pulmonary inflammation and fibrosis) observed in rats and mice exposed to single-walled CNTs (SWCNTs) and MWCNTs (NIOSH, 2010c), some types of MWCNTs have been shown to induce mesothelioma in rats (Fischer 344/Brown Norway F1 hybrids) by intraperitoneal injection (IP) (either 0.5 or 5 mg MWCNT/rat, twice with a 1-week interval) (Nagai *et al.*, 2011). In contrast, cancer was not observed in Wistar

Table 5. Human-equivalent benchmark concentration estimates for multiwall CNT, associated with estimated 10% excess risk in rat subchronic inhalation studies (NIOSH, 2010c).

Study	Reponse	Working lifetime 8-h TWA (μg m^{-3})
Deposited lung dose		
MaHock *et al.* (2009)	Granulomatous inflammation	0.48 (0.19)
Pauluhn (2010a)	Alveolar–interstitial thickening	0.8 (0.41)
Retained lung dose		
MaHock *et al.* (2009)	Granulomatous inflammation	2.7 (1.0)
Pauluhn (2010a)	Alveolar–interstitial thickening	3.5 (1.6)

Note: The upper LOQ of analytical method to measure elemental carbon is 7 μg m^{-3} (NIOSH Method 5040).
*Maximum likelihood estimate and 95% LCL.

rats 24 months after IP administration (2 or 20 mg/rat) of short MWCNT (<1 μm), although a clear carcinogenic response (~35% vs. ~4% in vehicle control) was observed at a 2 mg/rat dose of UICC crocidolite (Muller *et al.*, 2009). Likewise, pulmonary inflammation was observed in mice following IP of long (5–20 μm), thin, rigid CNT, but not of short or tangled CNT (<1 μm), suggesting a biological response consistent with the fiber paradigm (Poland *et al.*, 2008; Murphy *et al.*, 2011; Osmond-McLeod *et al.*, 2011).

Recent *in vitro* studies have observed specific genotoxic effects and associated biological mechanisms from certain MWCNTs and SWCNTs (Sargent *et al.*, 2009; Sargent *et al.*, 2011a,b). Significant spindle disruption and chromosome abnormality (aneuploidy) were observed at a low mass dose (0.024 μg SWCNTs cm^{-2} cells). Moreover, the SWCNTs were seen to be integrated with the DNA and the microtubule structures (Sargent *et al.*, 2011b). A high death rate occurred initially after the exposure to SWCNTs in both immortalized normal human bronchial epithelial cells (BEAS-2B) and primary normal human small airway epithelial cells (SAEC), followed by an increase in cell proliferation rates, which suggests an increased probability of passing on the genetic damage (aneuploidy) to daughter cells. Aneuploidy is a key event in the progression of some cancers (Kops *et al.*, 2005), and similar biological mechanisms have been observed with chrysotile and crocidolite asbestos (Cortez *et al.*, 2011; Yegles *et al.*, 1995). In addition, micronuclei (chromosome fragments that are not incorporated into the nucleus at cell division) were observed *in vitro* in cells (SAEC) that were incubated with carbon nanofibers (CNF), crocidolite asbestos, or SWCNTs (Kisin *et al.*, 2011). Micronucleated pneumocytes were also observed in rats after a single intratracheal dose of MWCNTs (Muller *et al.*, 2008). K-ras gene mutations, which have been reported in some lung tumors in humans and mice (Jackson *et al.*, 2006), were observed in mouse lungs following inhalation exposure to SWCNTs (Shvedova *et al.*, 2008).

These studies provide compelling evidence that at least some forms of CNT are potentially carcinogenic to humans. Typically, carcinogen classifications by authoritative bodies (e.g. International Agency for Cancer) have been based on human evidence or on chronic bioassays done in rats or mice (e.g. US National Toxicology Program, NTP). A key question for nanotechnology (and OSH generally) is how the findings from the biomechanistic studies should be interpreted in cancer classification decision-making. In view of the CNT evidence, a recent paper asks what specific actions should be taken now to protect workers before chronic animal bioassay data become available (Schulte *et al.*, 2012). Clearly, a high level of exposure containment and control would be prudent, especially for the thin, rigid CNT structures. Development and validation of a QSAR model to predict cancer potential based on CNT structure is a key research need; however, standardized, quantitative dose–response data are generally not yet available.

In addition to CNT, other chemical forms (e.g. metal compounds) and fiber-like (high aspect ratio) structures (e.g. nano rods and wires) are being developed for an array of nanotechnology applications. Understanding the properties influencing the cancer potential may facilitate the development of safer nanomaterials by design (Donaldson *et al.*, 2010).

Exposure measurement and control

Some of the NIOSH NTRC field research team studies have reported relatively large reductions in the airborne particle exposures after installation of standard engineering controls (NIOSH, 2010a). For example, during nanometal oxide reactor cleanout, the average percent reduction in airborne particulate was 96(±6)% based on particle counts or 88(±12)% based on particle mass by use of local exhaust ventilation (Methner, 2008). In a laboratory case study, the use of benchtop enclosures prevented the release of carbon nanoparticles during sonication (Johnson *et al.*, 2010). The enclosure was placed on a ventilated benchtop (100 ft min^{-1}). Before installation of exposure controls, airborne MWCNT bundles were observed by transmission electron microscope (TEM), and none were detected in the samples collected after the enclosure was installed (Johnson *et al.*, 2010).

A study of laboratory fume hoods showed that the hood design affects the nanoparticle release, and an air-curtain hood design (with a different airflow pattern) significantly reduced workers' exposures (Tsai *et al.*, 2010). A study of the filtration performance of a NIOSH N95 respirator showed that it meets the NIOSH respirator certification criteria (>95% filtration efficiency), although the most penetrating particle size was 50 nm in diameter (~2% filter penetration) (Rengasamy and Eimer, 2011).

Investigation of nanotechnology workers' health

NIOSH and others recommend evaluation of the need for medical monitoring of nanotechnology workers, as well as consideration of exposure registries, and development of epidemiological studies

(Nasterlack *et al.*, 2008; Schulte *et al.*, 2008; NIOSH, 2009a,b; Schulte and Trout, 2011; Boutou-Kempf, 2012). NIOSH recently began a study of US workers in facilities that produce or use engineered carbon nanoparticles (Dahm *et al.*, 2011; Schubauer-Berigan *et al.*, 2011), which included identification of the eligible companies and the most feasible population for study, followed by characterization of workers' exposures to CNT and CNF in manufacturing and distribution. These exposure data include respirable particle mass, number, and active surface area; personal full-shift daily exposure; and targeted sampling of the tasks associated with the highest exposures. Among the 30 companies (of the 61 eligible) that completed a questionnaire, the workforce size was >620, with 2–100 workers per company. Most (60%) of the operations were full scale, and another ~20% were planning to scale-up within 5 years. The materials produced and used included ~70% CNT and ~30% graphene, fullerenes, or carbon or polymer nanofibers. Assessing the health of nanomaterial workers is a critical component of responsible development of the technology (Schulte *et al.*, 2008; Schulte and Trout, 2011; Schulte *et al.*, 2012).

STRATEGIC GOALS: WHAT WE STILL NEED TO KNOW

Key questions concerning working with nanomaterials include the following:

- Are workers being protected?
- Are we effectively translating the research findings into workplace practice?
- Are occupational health guidance and standards keeping pace with the development of new nanomaterials?
- Are we effectively communicating the health risks and protective measures?

To the extent that the current OSH guidance is being followed, it would be expected to result in reduction or elimination of workers' exposures to engineered nanoparticles and potential adverse health effects. Thus, exposures of workers (e.g. to airborne asbestos fibers in textile manufacturing) that have occurred historically would need to be prevented in the production and use of nanomaterials (e.g. CNTs that are used to make high-strength fibers) (Fig. 3). Yet, to fully realize OSH goals for nanotechnology workers, more specific and verified information and guidance (Table 2), as well as measures to implement exposure control solutions in the workplace (Table 3), is needed. Development of more specific guidance on exposure control strategies (e.g. by process and task) is an example of translating research to practice (e.g. Methner *et al.*, 2008; NIOSH, 2009a; Tsai *et al.*, 2010). Such information may be especially helpful to workers and employers in research laboratories and small pilot operations that may not have dedicated OSH programs. Control banding strategies provide a useful decision logic for the initial selection of exposure controls (Paik *et al.*, 2008; ANSES, 2010). Validation of the effectiveness of these exposure control recommendations, and refinement as needed, is also an essential step.

Research needs for nanomaterials risk assessment

The value of information in risk assessment depends largely on the extent to which it reduces uncertainty in the risk estimates (Fig. 2). If a parameter does not have a large influence on the risk estimates, then a higher degree of uncertainty may be acceptable. However, if a risk estimate is highly dependent on a given assumption, then a greater level of effort or research priority in that area would be of value by improving the utility of the risk characterization.

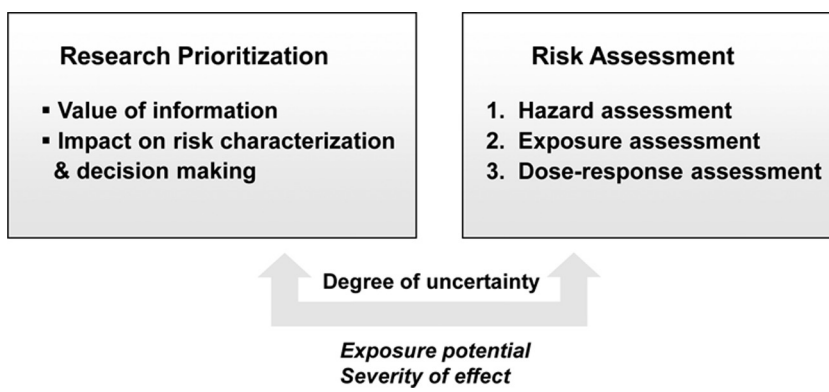

Fig. 2. Focused interaction between risk assessment and research needs.

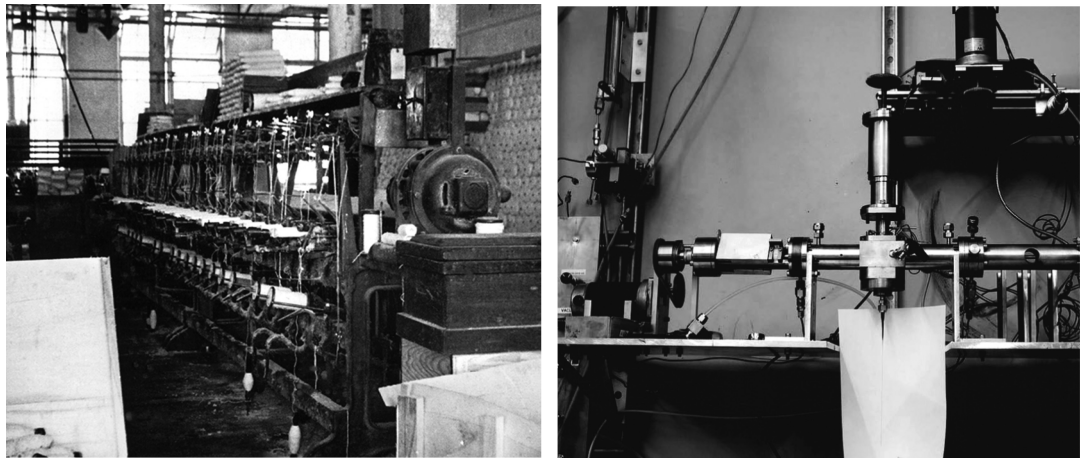

Fig. 3. Comparison of spinning operations for asbestos or CNT. (3a) Asbestos thread-making machine with spools of asbestos thread (c. 1930–1960). [Source: Public Health Image Library. Available at: phil.cdc.gov/phil/home.asp (ID#:9646)] (3b) Spinning SWCNT into high-strength 'super rope' fibers (early 2000s) [Source: Ericson *et al.* (2004). Reprinted with permission from American Association for the Advancement of Science (AAAS)].

Cross-cutting research needs. Risk assessment models and methods for various types of inhaled particles share some of the same steps, including (i) lung dose estimation, (ii) interspecies normalization (scaling) of dose, and (iii) temporal extrapolation of dose and response. Research and standardized approaches to reduce the uncertainty in these estimates would be useful for estimating risk and deriving exposure limits for CNTs and other nanomaterials.

Standardized testing. To facilitate comparison of results across studies and particle types, standardized assays and response endpoints are needed. Standardized assays and tiered testing approaches have been recommended (Oberdorster *et al.*, 2005b; OECD, 2008, 2010b), yet a relatively small number of the toxicology studies of nanomaterials provide sufficient data for risk assessment, and only a very few studies provide comparable dose–response data that can be evaluated across studies and particle types (NIOSH, 2010c).

Evaluation and validation of these assays for nanomaterials are also necessary. For example, for CNT, the fibrotic response may not be well predicted by pulmonary inflammation, as it may resolve at dose levels that nonetheless are associated with persistent alveolar septal thickening and fibrosis (Shvedova *et al.*, 2005, 2008; Pauluhn, 2010; Mercer *et al.*, 2011). The fibrotic mechanism may be related to the very thin, long CNT structures that mimic the epithelial basement membrane and stimulate fibrotic cell growth (Wang *et al.*, 2010).

Exposure measurement and control. Two challenges for future research include (i) demonstration of the effectiveness of reapplying proven control technologies from other industries (such as pharmaceuticals, cosmetics, and dry powder detergents) that are capable of achieving a high level of exposure control (e.g. in the microgram per cubic meter range), and (ii) until more sensitive and specific analytical methods are developed, background contributions must be factored into any nanomaterial exposure assessment strategy developed by a professional industrial hygienist. Effective risk communication is essential to translate research to risk management practice.

Categorical approach to OELs

Given the vast number of substances that require testing, alternative test methods are needed to increase the database for evaluating the hazard and determine the level of exposure control needed. Specifically, data that permit selection among the exposure control options are needed. For example, *in vitro* and cell free test methods have been developed using assays of cytotoxicity or reactive oxygen generation (Rushton *et al.*, 2010; Donaldson *et al.*, 2008). These current assays are useful for initial screening and priority setting for subsequent testing, although further evaluation of the association between *in vitro* and *in vivo* responses is needed before *in vitro* assays could fully replace standard *in vivo* assays (Landseidel *et al.*, 2010). A combination approach may also be feasible, by using existing animal dose–response data for well-characterized benchmark particles (for which risk has been quantified), along with short-term

in vivo or *in vitro* assays of an array of nanomaterials with similar chemical–physical properties and biological mode of action (e.g. carbonaceous particles; metal oxides) (Kuempel *et al.*, 2007, in preparation). The comparative toxicity data could then be used in a parallelogram type of analysis (Schoeny and Margosches, 1989; Sobels, 1993) to infer the risk by the nanomaterial in comparison to the benchmark particle. Development and evaluation of categorical approaches to support OEL development is a priority area of the NIOSH NTRC strategic plan (NIOSH, 2010b).

CONCLUDING REMARKS

Although there is uncertainty in the risk assessment of nanomaterials, it can be characterized to some extent. An evaluation of the main steps in the risk assessment process for inhaled particles shows which steps and assumptions have the largest influence on the risk estimates. This evaluation identifies the type of study data needed to reduce the uncertainty and the research priorities needed to obtain those data. Some of these steps involve uncertainty that is specific to the nanomaterial (e.g. CNT lung clearance), and some are more broadly applicable (e.g. extrapolating animal dose to humans; role of dose rate on the adverse effect). Other information is relatively well known (e.g. deposition fraction of inhaled particles in the respiratory tract regions, given the breathing parameters and the airborne particle size). Targeted research using standardized test methods and response endpoints would facilitate comparative toxicity assays and reduce uncertainty in risk assessment across nanomaterials. In addition to inhalation exposure (the focus of this article), dermal and other potential routes of exposure to nanomaterials in the workplace should be evaluated, as well as other possible effects beyond the lungs (NIOSH, 2009a; 2010b).

Considerable variability exists in the types of nanomaterials, including in the chemical composition, structure, and functionalization. Yet there are relatively few options for exposure control. Determining in which hazard and control 'bins' a nanomaterial fits may be feasible with relatively little data compared to the data needed for a full risk assessment and individual OEL. For example, additional information may be obtained through comparative toxicity to benchmark (reference or control) particles. Such a strategy may also facilitate comparison across particle types and development of safer nanomaterials. A key challenge, in order for nanotechnology to deliver on its promise of societal benefit, is to ensure that protection of workers' health is being met. Implementing effective measures to reduce or eliminate occupational exposures is an early step in a responsible life-cycle approach and the primary approach needed to prevent adverse health effects in workers producing or using nanomaterials.

SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

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