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Workshop Report

Workshop report: Strategies for setting occupational exposure limits for engineered nanomaterials

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ABSTRACT

Occupational exposure limits (OELs) are important tools for managing worker exposures to chemicals; however, hazard data for many engineered nanomaterials (ENMs) are insufficient for deriving OELs by traditional methods. Technical challenges and questions about how best to measure worker exposures to ENMs also pose barriers to implementing OELs. New varieties of ENMs are being developed and introduced into commerce at a rapid pace, further compounding the issue of OEL development for ENMs. A Workshop on Strategies for Setting Occupational Exposure Limits for Engineered Nanomaterials, held in September 2012, provided an opportunity for occupational health experts from various stakeholder groups to discuss possible alternative approaches for setting OELs for ENMs and issues related to their implementation. This report summarizes the workshop proceedings and findings, identifies areas for additional research, and suggests potential avenues for further progress on this important topic.

Certain engineered nanomaterials (ENMs) such as amorphous silica, zinc oxide, carbon black, and titanium dioxide have been used for many years, and considerable progress has been made in understanding and managing their occupational health risks. Over the past decade, however, many new, increasingly complex ENMs have been developed and introduced into commerce including those having unique chemistries (e.g., CdSe quantum dots, ZnGaN), surface modifications (e.g., organosilane- and acrylate-treated silicas), shapes (e.g., carbon nanotubes, Silica Nanosprings™) and other properties. Evaluation of the potential health risks posed by these

Occupational exposure limits (OELs) are widely recognized as valuable tools for managing worker exposure to chemicals and other hazards in the workplace. Most OELs are time-weighted average (typically 8-h) air concentrations believed to represent a safe level of exposure for most workers over their working lifetime. Worldwide, OELs have been established by government regulatory agencies, non-regulatory authoritative bodies, and chemical manufacturers for approximately 6000 substances. In contrast, no regulatory OELs and only a handful of non-regulatory and manufacturer OELs have been published for ENMs, the main reason being the lack of long-term animal inhalation toxicity data and epidemiology data which have traditionally served as the bases for setting OELs.

For an OEL to be useful, a validated and practical method for measuring airborne concentrations in the workplace must be available. Although instruments and techniques are available to measure airborne ENMs, they tend to be less portable, more complicated to

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operate, and more expensive than equipment used to monitor other substances. These and other technical issues, including uncertainties about the most relevant exposure metric and how to distinguish the ENM of interest from other particles in the workplace air, pose additional barriers to establishing and implementing OELs for ENMs.

A Workshop entitled "Strategies for Setting Occupational Exposure Limits for Engineered Nanomaterials" was held in September 2012 to provide an opportunity for occupational health experts and other interested stakeholders from industry, academia, government, and non-governmental organizations to discuss possible alternative strategies for setting OELs for ENMs and issues related to their implementation. The workshop agenda and invited speaker's slides are available at http://nanotechnology.americanchemistry.com/OELWorkshop.

This report is a summary of the workshop proceedings. It is not a comprehensive review of the scientific literature on OELs for ENMs, although citations are provided for the reader interested in additional details about specific approaches for setting OELs and other topics discussed at the workshop. Ideas and concepts for which there appeared to be general agreement among workshop attendees were identified, but no effort was made to reach group consensus on any topic. Therefore, this report should not be viewed as reflecting the opinion of all workshop participants, their affiliated organizations, or the workshop sponsors or organizers.

2. Workshop findings

2.1. The need for occupational exposure limits for ENMs

There was broad agreement on the need for OELs for ENMs and that they should be established before health effects might begin to emerge among exposed workers. Standard industrial hygiene measures such as ventilation, containment, respirators, and other personal protective equipment (PPE) are considered effective for controlling occupational exposures to ENMs and can be employed in the absence of OELs. However, unnecessary use of these measures is costly, reduces worker efficiency, and, in some instances, may paradoxically increase the likelihood of workplace injuries such as musculoskeletal disorders associated with the use of glove boxes (UKHSE, 2012). Due to the rapid pace at which new ENMs are being developed, setting OELs for them cannot be a process driven solely by government agencies, nor can non-regulatory authoritative bodies such as NIOSH and ACGIH be expected to fill the void. Rather, OEL development for new ENMs will need to be a collaborative effort between manufacturers, regulatory agencies, and non-regulatory organizations. In light of the limited published hazard data available for most new ENMs, a conservative approach is warranted in setting and using OELs for them.

2.2. Barriers to developing OELs for ENMs

The lack of adequate published toxicity data, especially from long-term animal inhalation and worker epidemiology studies, is the primary barrier to developing OELs for most ENMs. Exceptions are the substantial quantities of toxicity data available for certain "first generation" ENMs such as titanium dioxide, amorphous silica, carbon black, and zinc oxide, and for some carbon nanotubes (CNT). Due to the number and varieties of new ENMs being developed and the time and resources required to perform long-term inhalation and epidemiology studies, it appears unlikely that these types of data will be generated for most new ENMs. There is a clear need for faster, more cost-effective methods for assessing the toxicity of new ENMs and for new strategies for deriving OELs based on more limited toxicity information.

Developing OELs for ENMs is also hampered by our limited current understanding of how the physicochemical properties of ENMs influence their *in vivo* kinetics and toxicity relative to that of their larger counterparts. A challenge in comparing ENMs to their larger counterparts or to other ENMs in a similar physicochemical class is that more than one property is sometimes changed at the same time as size, e.g., surface chemistry, surface area, or crystal phase. At a fundamental level, the properties considered to be most relevant to the toxicology of ENMs include size, size distribution, shape, agglomerate/aggregate state, density, surface area, surface charge, surface reactivity, solubility, and crystalline phase. The combined interactions of these properties, and undoubtedly others, determine the dose–response patterns observed in toxicology studies with ENMs. While quantitative property–toxicity relationships have been reported for certain ENMs under specific experimental conditions, no general rules have yet been established by which the chronic toxicity of ENMs can be accurately predicted based on physicochemical property information alone. Nonetheless, measuring and reporting appropriate physicochemical property information for ENMs evaluated in toxicity studies is considered essential to developing a deeper understanding of property–toxicity relationships for ENMs and for comparing findings among studies and laboratories.

A third factor impeding the development of OELs for ENMs is uncertainty concerning the most relevant dose or exposure metric. With the exception of fibrous materials such as asbestos, virtually all existing OELs for particulate materials are mass-based with units of mg/m^3, and they are usually based on toxicity data in which doses are expressed as an airborne mass of material. In the case of ENMs, however, animal inhalation and intratracheal instillation studies have found correlations between toxicity and administered doses expressed as particle mass, surface area, number, density, and volume. This diversity of dose metrics is perhaps not surprising considering the diversity of study designs, ENMs, and toxicity endpoints evaluated in these studies, but it creates uncertainty in interpreting toxicity data and in developing methods for measuring workplace exposures. Ongoing research may eventually clarify this matter, but, in the meantime, mass-based sampling and related analytical methods are viewed, at least within the U.S., as the most practical means for routinely monitoring airborne particulates in the workplace, and this is expected to drive OEL development for ENMs towards mass-based values, as least in the near-term.

Finally, the lack of standardized and validated methods for monitoring workplace concentrations of ENMs hinders the development of OELs and vice versa. Not only must such methods be capable of size- and substance-specific detection of low airborne concentrations, they must also be able to distinguish the ENM of interest from background levels of other particles which are almost always present in the workplace air. Conversely, the lack of OELs against which air monitoring data can be interpreted lessens the impetus for conducting air monitoring and for developing practical methods for measuring ENMs.

2.3. Strategies for setting OELs for ENMs: traditional and alternative approaches

Various approaches for setting OELs for ENMs have been used or proposed (reviewed in Schulte et al. (2010) and van Borekhuizen et al. (2012)). These approaches fall into two broad categories based primarily on the availability of toxicity data. When adequate toxicity data for the ENM are available, traditional quantitative risk assessment (QRA) methods have been used to set specific numerical OELs. When toxicity data for the ENM are limited, as is more often the case, alternative pragmatic approaches based on general principles and professional judgment have been used. Examples of

several alternative approaches and their perceived advantages and limitations were discussed at the workshop as summarized in the following sections.

2.3.1. Traditional quantitative risk assessment methods

Traditional QRA methods for setting OELs typically involve reviewing available toxicity data to identify a critical adverse effect, selecting a dose – usually a no-observed-adverse-effect-level or benchmark dose – to use as a point of departure, calculating a human equivalent concentration, and applying various uncertainty and modifying factors. Refinements of this general approach for setting OELs for inhaled particles have been described (Oberdörster, 1989; Kuempel et al., 2006). The European Chemicals Agency (ECHA, 2010) has established guidelines for calculating chronic inhalation derived-no-effect-levels (DNELs) for workers that are based on the standard QRA approach and are currently being used in registrations of chemicals, including ENMs, in Europe. Examples of ENMs for which OELs have been derived using variations of the standard QRA approach include titanium dioxide (NEDO, 2009; NIOSH, 2011; Stone et al., 2010) and carbon nanotubes (Luizi, 2009; Pauluhn, 2010; Stone et al., 2010; NIOSH, 2013).

Traditional, substance-by-substance QRA methods have a long history of use and were generally viewed by workshop participants as the most scientifically valid approach for setting OELs for substances for which sufficient toxicity data are available. Since few ENMs have sufficient published toxicity data to permit the use of QRA methods, most of the workshop focused on alternative approaches. It is worth noting, however, that while OELs established by QRA methods are often considered to be more precise than OELs established by alternative approaches, OELs established by different groups for the same ENM using QRA methods often vary by orders of magnitude. For example, recommended OELs for nano-TiO_2 include 0.017 mg/m^3 (Stone et al., 2010), 0.3 mg/m^3 (NIOSH, 2011), and 1.2 mg/m^3 (NEDO, 2009). Such differences arise from differences in the interpretation of the supporting toxicity data, selection of points of departure, and use of uncertainty and modifying factors. Professional judgment thus plays a significant role in setting OELs even by traditional QRA methods.

2.3.2. Control banding

The ultimate goal of control banding is not to derive precise OELs, but to select from among a limited set of available exposure control techniques those that will most effectively protect the health of workers. Several control banding approaches for ENMs have been proposed (e.g., Maynard, 2007; Paik et al., 2008; Schulte et al., 2008). In these approaches, recommended exposure control measures such as ventilation, engineering controls, or containment are identified based on criteria related to the probability of exposure (e.g., dustiness, amount used, exposure duration) and the probability of an adverse health outcome (e.g., known hazards of the material, surface area, shape). Most banding approaches do not provide numerical airborne concentrations that can be used as benchmarks for evaluating air monitoring data or the effectiveness of control measures.

2.3.3. Adjustments to existing OELs for corresponding coarse and fine particulates

Several methods for setting OELs for ENMs involve the application of adjustment or safety factors to existing OELs for the corresponding coarse and fine particulate materials. The British Standards Institute (BSI, 2007) proposed setting Benchmark Exposure Levels for ENMs by applying defined safety factors of 0.5 for soluble ENMs, 0.66 for poorly soluble ENMs, and 0.16 for ENMs presumed to be carcinogenic, mutagenic, asthmatogenic, or reproductive toxins to existing OELs for the larger materials. Kuempel et al. (2007) described a conceptual approach for setting OELs for ENMs in which an existing OEL for the larger material is divided by factors reflecting differences in specific surface area, pulmonary deposition fraction, and surface reactivity for the fine- and nano-sized forms of the material. The Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2009) has recommended that an appropriately derived OEL for a soluble material can be used without modification as a provisional Nano Reference Value for ENMs that are not biopersistent and not fibrous.

Despite the apparent logic of applying adjustment factors to existing OELs for larger particulate materials to derive OELs for the corresponding ENMs, there was a general lack of agreement among workshop participants about whether it is appropriate to do so or how to make these adjustments. Approaches which apply adjustment factors based on measured differences in biologically relevant properties of the fine- and nano-sized forms of a specific material, such as the conceptual approach of Kuempel et al. (2007), seem reasonable; however, workshop participants generally felt that experiments to identify the most biologically relevant properties for a particular ENM and its larger counterpart should be performed before using this approach. Furthermore, many of the newer ENMs being developed do not have corresponding larger materials for which OELs have been established, thus limiting the overall utility of this approach.

2.3.4. Bridging or read-across of in vitro and short-term in vivo toxicity data

In vitro and short-term *in vivo* studies have been performed as relatively quick and inexpensive means of screening the toxicity of new ENMs. While these types of data have not traditionally been used to derive OELs, the lack of longer-term toxicity data for many ENMs has led to attempts to do so. Two examples of this approach were discussed at the workshop.

Maier (2011) described an *in vitro* read-across approach used to establish numerical, order-of-magnitude occupational exposure bands (OEBs) for unstudied pharmaceutical intermediates that might be adapted to ENMs. Briefly, this approach involves conducting side-by-side *in vitro* testing of the ENM and a structurally related, well-studied, positive control material having an OEL or for which an OEL could be derived. The *in vitro* test system, toxicity endpoints, and test article concentrations must be carefully selected for relevance to the ENM's anticipated hazards and workplace exposure levels. An OEB is selected for the ENM based on its *in vitro* potency relative to the positive control material and the OEL for the positive control material. In principle, the uncertainty inherent in relying on *in vitro* data in this approach is offset by the order-of-magnitude width of the OEBs. Nevertheless, as the author notes, it is important to recognize the limitations of this approach and to consider OEBs not as presumed safe levels of exposure but as limits which, if exceeded, should trigger the need for additional exposure control measures.

There was broad agreement on the value of *in vitro* studies to better understand the potential hazards of ENMs and their modes of action. However, it was not felt that bridging based on *in vitro* data alone, at least as these studies are currently performed, can be used to derive OELs which are adequately protective against potential hazards resulting from chronic inhalation of ENMs. To accurately extrapolate data from *in vitro* studies to *in vivo* exposures, measurements or estimates of the target cell dose are considered critical. In the absence of direct experimental measurements, these relationships may be derived using *in vitro* (Hinderliter et al., 2010) and *in vivo* (Anjilvel and Asgharian, 1995) particle dosimetry models. If *in vitro* data are to be used to develop OELs, it will also be necessary to identify corresponding *in vitro* and *in vivo* biological endpoints that are toxicologically relevant for health outcomes in exposed workers. Two suggested endpoints worthy of further consideration are markers of fibrogenicity and reactive oxygen species

(ROS) generation. Transcriptomics may be useful for identifying other *in vivo* endpoints which can be measured using *in vitro* models to define the minimal cell doses that stimulate specific biological pathways; however, pharmacokinetic influences should be taken into account. Any consideration of the use of *in vitro* data to derive OELs must be tempered with the understanding that, for exposed workers, multiple exposures are common, adaptation can occur, and adverse effects are often manifested only when normal homeostatic mechanisms are overwhelmed.

Warheit (2013) described a bridging approach to estimate OELs for three types of nano-TiO_2 based on comparative intratracheal instillation studies in rats. Toxicity profiles for the ENMs in these studies were compared with that for a control material (pigment grade TiO_2) for which an extensive database of long-term animal inhalation data and epidemiological data exists. Based on these comparisons, OELs of 1, 2 and 5 mg/m^3, respectively, were estimated for high-surface-reactivity anatase–rutile nano-TiO_2, low-surface-reactivity nano-TiO_2, and pigment-grade TiO_2.

Bridging based on comparative intratracheal instillation study data seemed to represent an acceptable compromise between the need for faster, less-costly methods for evaluating the toxicity of ENMs and the long-term inhalation study data typically needed for setting OELs by traditional methods. The limitations of intratracheal instillation studies have been described (Driscoll et al., 2000) and will not be repeated here. However, by bridging to a well-studied control material for which long-term inhalation data are available, these limitations can be at least partially mitigated. Discussion of this approach focused primarily on study design considerations. In addition to including appropriate positive and/or negative particulate controls, it was generally agreed that intratracheal instillation studies of ENMs should include robust test substance characterization, dose–response data, a time-course assessment (e.g., 1 day, 1 week, 1 month, and 3 months post-exposure), and that doses should be relevant to potential worker exposures and not so high as to cause lung overload. Furthermore, dose bridging between instillation and inhalation should be done in terms of deposited lung doses, derived either via direct measurements or model estimates.

2.3.5. Occupational benchmark based on an ambient air standard for fine particulates

Various governments have promulgated ambient air quality standards for particulate matter based on historical data demonstrating associations between particulate air pollution episodes and health effects in exposed human populations. Guidotti (2010) has proposed a benchmark occupational exposure level of 30 μg/m^3 (8-h time-weighted average) for relatively inert ENMs such as TiO_2 based on a Canadian ambient air quality standard of 30 μg/m^3 (24-h average) for fine particulate matter ($PM_{2.5}$) (CCME, 2000). The Canadian standard is considered to be a reasonably conservative benchmark for occupational exposures since it represents an effective maximum allowable concentration (98th percentile of measurements over a 3-year period) for the general population, including susceptible individuals such as those with asthma and cardiovascular disease. The author suggests that the proposed benchmark might be used as a provisional regulatory standard until data become available to support more definitive OELs for individual ENMs.

Advantages of this approach are that it is based on a large historical database of epidemiology data concerning ambient particulate exposures in humans and it appears that the proposed benchmark limit would be adequately protective for workers exposed to relatively inert ENMs. On the other hand, many ENMs cannot be assumed to be relatively inert. For these ENMs, the author suggests the use of additional safety factors for properties such as metal content, fibrous shape, biological activity, and resemblance to known hazards; however, it is not clear how these safety factors would be determined or applied. A more serious concern is whether it is appropriate to use an ambient standard for fine (⩽2500 nm) particulates and apply it to ENMs (⩽100 nm) having different compositions and properties. Ongoing research into the contribution of ultrafine ambient particulate matter and specific components of the ultrafine fraction to observed health effects in the general population should help to clarify some of these questions.

2.3.6. Categorical approaches

Several authors have proposed benchmark OELs for categories of related ENMs. The BSI (2007) and IFA (2009) recommended a benchmark OEL of 0.01 fiber/cm^3 for certain insoluble or biopersistent nanofibers (e.g., carbon nanotubes) based on an existing OEL for asbestos. The IFA also recommended benchmark OELs of 20,000 particles/cm^3 above background for biopersistent granular ENMs with densities greater than 6000 kg/m^3 and 40,000 particles/cm^3 above background for biopersistent granular ENMs with densities less than 6000 kg/m^3 and for nanofibers for which asbestos-like toxicity can be excluded.

Kuempel et al. (2012) described a risk-based approach for setting OELs for ENMs based on potency comparisons to benchmark materials from various mode of action (MOA) classes. Four MOA classes were proposed: toxic ions reaching systemic tissues (i.e., higher solubility particles), surface area dose of respirable particles (i.e., poorly soluble, low-toxicity particles), reactive particle surface area dose (i.e., poorly soluble, high-toxicity particles), and fibrous particles for which toxicity is presumed to be related to biopersistence, migration to the lung pleura, and genotoxicity.

A third example of a categorical approach was described by Pauluhn (2011), who derived a generic OEL for poorly soluble, low-toxicity nanoparticles for which toxicity is presumed to be due to sustained pulmonary inflammation caused by overload-associated impaired alveolar macrophage clearance. According to the author's calculations based on data from 4- to 13-week inhalation studies in rats with several materials, lung overload begins to occur when airborne particulate concentrations exceed 0.54 μl/m^3. This volume-based airborne concentration is proposed by the author as a generic no-observed-adverse-effect-concentration (NOAEC) for poorly soluble, granular, low-toxicity particles in humans. Multiplying this NOAEC by the agglomerated particle density for a particular ENM yields the corresponding mass-based OEL. In this approach, necessary adjustments for differences in ventilation rate, fractional particle deposition, body weight, and particle clearance between rats and humans conveniently cancel out and thus do not appear in the final OEL calculation. By using this approach, it is argued, an adequately designed and executed subacute or subchronic inhalation study in rats can be used as the basis for deriving a chronic OEL for a poorly soluble, low-toxicity ENM. This approach would not be suitable for ENMs for which extrapulmonary effects predominate.

There was general agreement that categorical approaches hold promise as alternatives for deriving OELs for ENMs when sufficient data are not available to use traditional QRA methods. Potential advantages of categorical approaches for setting OELs include more efficient use of existing toxicity data, reduction in overall costs of toxicity testing and animal use, increased sample size, and less uncertainty concerning biological plausibility for substances within the same MOA or toxicity category. Given the number of factors that can influence the toxicity of ENMs and our current limited understanding about which factors are most important, narrower categories would be more supportable than broader ones. To group nanomaterials into MOA or toxicity categories that can be used to support categorical OELs, the key physicochemical properties that drive toxicity need to be identified. Some suggested properties

include: dissolution leading to toxicity by released ions, generation of ROS, fibrous shape, and hydrophobicity. By testing libraries of ENMs whose physicochemical properties vary incrementally, associations between physicochemical properties and MOA or toxicity categories can be established and ENMs can be ranked within these categories (e.g., Zhang et al., 2012; Rushton et al., 2010; Mercer et al., 2008).

2.4. Practical workplace challenges related to setting and using OELs for ENMs

Regardless of the approach used to generate OELs for ENMs, suitable instruments and procedures for measuring workplace concentrations are needed to assure confidence in recommending specific controls. ENMs are produced and used in a wide variety of occupational settings, including manufacturing facilities, pilot plants, laboratories, and clean rooms, each involving different types and quantities of ENMs, handling procedures, and exposure controls.

Airborne particles at nanotechnology facilities are not homogeneous, and significant background levels of natural and incidental particulates other than the ENM of interest are common. For example, the exhaust of a furnace used to produce CNTs by a chemical vapor deposition process was shown to contain spherical particles of carbon-encapsulated catalyst, carbon filaments, filament clusters, and CNT fibers and clusters measuring less than 500 nm (Tsai et al., 2009). In a study involving outdoor aerosol measurements, a field instrument was completely overwhelmed by nanoparticles from a diesel generator located 25 ft away (Ostraat and Chartier, 2011). In an exposure assessment of a silicon nanoparticle synthesis and packing process, it was shown that nanoscale particle counts were influenced by the heat sealing of polymer bags (Wang et al., 2012).

Other challenges are that standard operating procedures for assessing ENM exposures are not available and commercial monitoring equipment tends to be complicated to operate, not easily portable, and expensive. Sampling devices such as a modified filter-based sampler with attached transmission electron microscopy grids (Tsai et al., 2009), impactors, electrostatic precipitators, and thermal precipitators can be used to collect particles to analyze their morphology and elemental composition. However, the mechanics and metrics of these devices differ, creating challenges in comparing measurements made with different instruments (Jeong and Evans, 2009; Asbach et al., 2012). An ideal monitoring device for ENMs would be easily portable, permit an individual industrial hygienist to perform mass- and number-based assessments, have the ability to detect specific particle types with specified size resolution, and be low cost, simple to operate, and robust in diverse operating environments.

As part of its nanotechnology research agenda, NIOSH created a field studies team to assess workplace processes, materials, and control technologies at various nanotechnology facilities. The team used a holistic approach that included time-integrated air samples analyzed for elemental mass and for structure count by electron microscopy, wipe samples analyzed for elemental mass, and direct-reading instrument measurements. Time-integrated samples were collected in the worker's breathing zone, as area samples, and in non-production areas to characterize background levels. Wipe samples assisted in characterizing work practices that could lead to surface contamination and the potential for migration to other areas of a facility. Direct reading instruments provided supplemental information to assess efficacy of engineering controls, assess the potential of a specific process or task, and identify general increases or decreases in total particle concentration.

International efforts to harmonize nanomaterial exposure assessment strategies have been ongoing since 2009 (Brouwer et al., 2012). Preliminary recommendations have included the use of a multimetric, tiered approach to exposure assessment with identified minimum sets of exposure and contextual data to be collected for initial assessments, simplified measurements, and in-depth assessments. Different strategies will be necessary for high aspect ratio nanotubes and nanofibers for which different instrumentation is used. Other issues needing further research include statistical approaches for analyzing time-series data, a standardized approach to electron microscopy analysis and reporting, and a database to store and merge data.

3. Conclusions and recommendations

As stated in Section 1, no effort was made to reach group consensus on any topic discussed at the workshop, and this report should not be viewed as reflecting the opinion of all workshop participants. Nevertheless, there appeared to be general agreement among workshop attendees on a number of ideas and concepts listed below.

3.1. General conclusions and recommendations

- Scientifically robust, published OELs for ENMs are urgently needed.
- It is unlikely that sufficient toxicity data will be available for most new ENMs to allow traditional QRA approaches to be used to set OELs.
- An iterative approach in which initial provisional OELs or bands are established and adjusted as additional data become available is seen as a rational path forward.
- Standard industrial hygiene measures are effective for controlling occupational exposures to ENMs, even in the absence of OELs; however, the absence of OELs can lead to unnecessarily restrictive control measures and limits the ability to evaluate the effectiveness of the controls.
- Due to the rapid pace at which new ENMs are being created, OEL development for ENMs needs to be a collaborative effort between manufacturers, regulatory agencies, non-regulatory organizations, and other stakeholders, as well as between toxicologists, industrial hygienists, epidemiologists, occupational physicians, and material and analytical scientists.
- In light of the limited hazard data available for most new ENMs and our limited current understanding of the factors that influence their biological behavior, a conservative approach is warranted in setting and using OELs for ENMs.
- There is a clear need for faster, more cost-effective methods for evaluating the toxicity of new ENMs.
- Doses used in toxicity studies of ENMs should include anticipated human exposures, when known. Effects that occur at extremely high doses may mask effects at occupationally relevant doses.
- There is a need to utilize more fully the knowledge gained from studies performed on older, first-generation nanomaterials and ambient particulates in evaluating newer ENMs.
- When available, medical surveillance data (e.g., chest x-rays, pulmonary function tests) for workers exposed to ENMs should be considered in setting OELs.
- More consideration should be given to potential extrapulmonary effects that could drive OELs for certain ENMs.
- The most toxicologically relevant dose or exposure metric for ENMs has not been established. Different dose metrics may be relevant for different ENMs, study designs, and toxicity endpoints. However, at least in the U.S., mass-based sampling and analytical methods are currently considered the only practical means for routine monitoring of airborne particulates in the workplace.

- There is a need for more practical sampling and analytical instruments and standardized procedures for conducting exposure assessments of ENMs in workplaces.
- More consideration of potential worker exposures to ENMs throughout the product life-cycle, including disposal/recycling, is needed, as well as adequate communication of known hazards to potentially exposed workers.
- Greater transparency and documentation of how OELs are derived for specific ENMs is important.

3.2. Regarding specific approaches for setting OELs for ENMs

- Traditional, substance-by-substance, QRA methods are considered to be the most scientifically valid approach for setting OELs for ENMs when sufficient toxicity data are available to do so. Nonetheless, different policies and procedures used by different organizations can result in very different OELs for the same material. These policies and procedures should be clearly described in the OEL documentation.
- There is no single best alternative approach for setting OELs for ENMs. Several of the approaches discussed at the workshop may be appropriate depending on the specific properties of the ENM, the types of toxicity data available, whether an OEL exists for the larger material, whether the OEL is intended to be a non-regulatory provisional value or a regulatory limit, and other considerations.
- Approaches in which adjustment factors are applied to an existing OEL based on measured differences in biologically relevant properties of the fine- and nano-sized forms of the material seem appropriate; however, studies should be performed to identify the most biologically relevant properties before using this approach.
- Methods for setting chronic OELs for ENMs based on *in vitro* data or ambient air quality standards for fine particulates are not sufficiently developed to recommend their general use at the present time; however, these approaches may have value in selecting provisional exposure control measures.
- Bridging based on well-designed intratracheal instillation studies in rats with a suitable control material for which long-term inhalation data are available (Warheit, 2013) appears to be an appropriate approach for setting OELs for certain ENMs.
- Categorical approaches based on potency comparisons to benchmark materials from various mode of action classes (Kuempel et al., 2012) and for poorly soluble, low-toxicity nanoparticles for which toxicity is related to lung overload (Pauluhn, 2011) hold promise for deriving OELs for ENMs and should be further developed.

3.3. Recommendations for further research and collaborations

- Refinement and standardization of *in vitro* methods and models for evaluating ENMs, for example by using alveolar tissue and incorporating deposited dose metrics.
- A standard set of particle descriptors, dose metrics, and endpoints for comparing mode of action and dose–response data across studies.
- Predictive models for correlating short-term to long-term *in vivo* response to ENMs.
- Identification of susceptible worker sub-populations.
- Health risks posed by exposure to mixtures of ENMs.
- Exposure potential throughout the product life cycle, including disposal/recycling.
- Development of a decision logic for an iterative process of establishing OELs for ENMs which might, for example, involve setting provisional OELs based on *in vitro* and/or short-term *in vivo* mode of action data followed by confirmatory longer-term animal studies and revision of the provisional OEL.
- Additional government funding for traditional long-term inhalation toxicity studies on selected ENMs.
- Collaborations with other international organizations including ISO and OECD.
- Convening roundtable discussions at professional meetings such as the Society of Toxicology (SOT), the American Industrial Hygiene Association (AIHA), and the International Society of Environmental Exposure (ISEE).
- Creating an organization, perhaps modeled after the Occupational Toxicology Roundtable, for the purpose of holding regular (annual) follow-up meetings.
- Improved understanding of toxicokinetics, dose metrics for extrapolating data from *in vitro* and short-term animal studies to humans, and associations between physicochemical properties and biological activity.

Conflict of interest

The authors declare that there are no conflicts of interest.

Disclaimer

The individual authors do not necessarily represent the views or policies of their institutions nor endorse all statements herein.

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