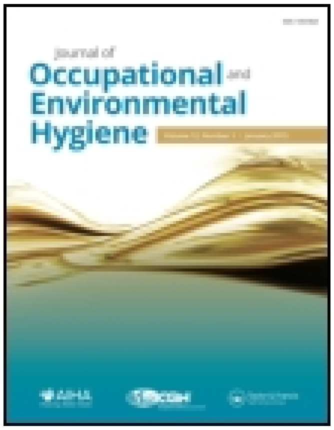

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Achieving Control of Occupational Exposures to Engineered Nanomaterials

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Occupational exposures resulting from Engineered Nanomaterials (ENMs) can pose a challenge for applying traditional risk assessment, control, or evaluation standards. This article discusses the limitations in traditional risk management approaches when it comes to ENM exposures, reviews current monitoring options, and suggests an interim management framework until research can meet the standard of evidence required by legislators. The proposed Nanomaterial Occupational Exposure Management Model (NOEM) offers a pragmatic approach that integrates resources from current academic research to provide a framework that can be applied by both industry and regulators. The NOEM Model focuses on addressing three concerns to exposure management: Risk Assessment, Exposure Control, and Exposure Monitoring. The resources supported for meeting these three components involve the integration of the Control Banding Nanotool and Nano Reference Values, both of which have been piloted and accepted through peer-reviewed processes and industry consultation.

Keywords exposure assessment, framework, nano, nanomaterial, occupational

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/uoeh.

INTRODUCTION

The global use and applications of engineered nanomaterials (ENM) in commercial and consumer goods is rapidly increasing.(1–6) Moreover, although the uses of ENMs are varied, they are most often used to enhance product functionality by way of their unique characteristics such as high electron affinity, electrical conductivity, mechanical strength, large surface areas, and optical properties.(7) The use of these properties are not limited to a few sectors, but include various industries such as electronics, communications, materials, machinery, tools, construction, pharmaceuticals, health care, energy, environment, and water treatment.(3,4)

Although widely used, the scale of international growth of ENMs is difficult to trend as patents and investments are not discretely categorized in conventional registries.(4,6) It is has been proposed that the growth of future investments may slow due to uncertainty surrounding outcomes from occupational, public, and environmental ENM exposures.(4,6,8,9) Additionally, the emergence of increasingly advanced nanoapplications introduces concerns regarding novel mechanisms of action and their implications on health and safety from occupational exposures.(10,11) Therefore, the need for adaptive risk management strategies that are both precautionary and pragmatic has been recognized as a priority for the safe existing, and anticipated uses of ENMs.(1,2,8)

Multinational and collaborative organizations have developed strategies for prioritizing and anticipating research gaps in managing ENM exposures in workplace settings.(8,12) These organizations have structured research objectives to support traditional and comprehensive risk-based approaches for managing health and safety risks.(13) Priorities include the standardization of terminology, classification, safe handling, and testing parameters and methodologies.(4,6,8) Organizations supporting these needs include the British Standards Institute (BSI), the Organization for Economic Co-operation and Development (OECD), the World Health Organization (WHO), National Institute for Occupational Safety and Health (NIOSH), US National Nanotechnology Initiative (NNI), and the US Environmental Protection Agency (US EPA). In addition to these global initiatives, information dissemination is occurring at the jurisdictional levels closest to end-users. For instance, in Canada publicly funded web portals for nano-specific information are available in the provinces of Alberta, British Columbia, Ontario, and Quebec.

BACKGROUND

The barriers for establishing ENM risk management frameworks include the absence of consistent assessment and categorization parameters for ENM toxicity, as international testing standards are still being determined.(1,2,14) Despite this, research has progressed in the area through the continual refinement of traditional parameters in efforts to establish representative variables for health risk.

One of the fundamental properties of ENMs that raises concerns for exposure risk is size. The size range of ENMs (1–100 nm) makes the alveolar region the primary deposition site.[15] This is an added concern for ENM exposures due to the greater particle number, and therefore greater surface area to unit of mass, compared parent compounds.[16] The result is a potentially greater interaction of ENMs at the cellular level, at which point they can elicit defense mechanisms and adverse health effects.[17,18] Concerns centering on the size and surface area properties are also being raised in the potential for ENM translocation to other parts of the body, and their potential ability to pass through cellular membranes to interact with cell structures.[8,10]

Information on the size implications of ENMs has been amassed from *in vitro, in vivo*, and research of ultrafine particulates.[7] These studies have provided insight that has shaped the direction of research priorities for ENM occupational exposures by highlighting the unique challenges the size of ENMs presents for toxicity and exposure potential. For instance, lessons from the deposition of ultrafine particulates in the respiratory system are relevant in understanding equivalent behavior in ENMs that comes with the similarity in their physical size properties.[10,15,17] The understanding of the deposition fraction of ENM in respirable regions, however, is further complicated by ENM behavioral tendencies such as agglomeration and aggregation, which lead to particle interception in different respiratory regions as characterized by size differentiating defense mechanisms.[10,15,18] Findings such as these have been relevant for contrasting ENM with their bulk parent compounds for the purpose of assessing the suitability of conventional risk management strategies. Other factors that have been found to influence biological response include the particle solubility, shape, charge, surface chemistry, catalytic properties, and adsorbed pollutants.[19]

The diversity of ENMs in respect to their physiochemical properties is one of the primary challenges for managing occupational exposure risks.[6] Regulations pertaining to use of ENMs are limited in their provision of specific measures to be implemented and enforced. Traditional legislated occupational exposure management strategies are designed based on precautionary approaches rooted heavily in quantitative and verified research findings. The variables for comprehending and quantifying the health risks of ENMs are burdened with uncertainty as the conventional parameters and approaches are regarded as incompatible for addressing occupational ENM exposures.[5–8,11–13,20–29]

CONTROL METHODS

The conditions under which ENM exposures occur are widely varied.[30–32] The technology and mechanisms involved in the generation and application of ENMs varies depending on the material and the intended use.[33] This makes the assessment and control of occupational exposures a unique exercise specific to materials involved and the emission scenario.[2,32] Given the limited toxicological data compared to the vast number of ENMs and varied exposure scenarios, traditional occupational risk management resources have been strained in their capacity to address the parameters of ENM risk.

Occupational Exposure Limits

A principle occupational risk resource that is central to assessment and control strategy success is the metric for evaluating exposures. Conventionally, mass-based occupational exposure limits (OELs) serve as a standard against which exposures levels and control measures to chemical substances are evaluated.[28] As the mechanisms of ENM toxicity become increasingly better understood, mass-based exposure metrics are being recognized as a non representative universal parameter for evaluating exposure potential.[28,34] Properties such as the greater particle number and surface area of ENMs per unit of mass can pose greater potential for some ENMs due to their interaction with pulmonary and cellular structures, resulting in inflammation, oxidative stress, and other biological responses.[15–17,23,35] These findings suggest that parameters such as particle number and surface area need to be assessed for each ENM as to whether they provide a more relevant indicator of toxicity and may be more apt as exposure metrics than mass-based ones which fails to account for the surface reactivity.[5]

In addition to concerns on the suitability of the exposure metric, the standard of evidence that is needed to support the establishment of OELs for ENMs is being outpaced by the areas growth.[22,25,28] Barriers to meeting the quantitative risk assessment standard for OEL development includes the lack of comprehensive data on emerging ENMs, uncertainty on physiochemical properties, variability in exposure metrics, and the lack of standardized and validated monitoring strategies.[1,8,10,13,20,22] An alternative approach to managing exposures is through the application of categorical exposure limits based on benchmarks.[22,23,28,36]

Benchmarking uses a reference material as a standard for the comparing other materials with similar modes of action. A categorical approach for setting exposure levels can guide the evaluation of similar materials, despite the limitations in the information on the materials toxicity.[23,28] Currently, based on benchmark and equivalent tissue doses, adequate data sets exist to establish recommended exposure levels for materials such as carbon nanotubes and nanofibers (1.0 $\mu g/m^3$), titanium dioxide (0.3 mg/m^3), and fullerenes (0.8 mg/m^3).[26,27,34,37] The variety of ENMs in use is broader than those with robust data sets to support specific exposure levels, thus benchmarking is supported as an adaptive system to manage emerging risks when toxicological data is lacking.[29]

Control Banding

By using a semi-qualitative approach, control banding uses a combination of the health hazard and exposure potential to identify a suitable band to which general control measures are appropriate.[38–40] Depending on the application, the specified bands and assigned controls may vary, although it has been accepted that four control bands balance ease of use with established and accepted control measures.[41] Alternate utilizations for control banding have stemmed from its simplicity, including its adoption into the pharmaceutical industry for controlling risks from novel product exposures.[39,42] Lessons from controlling novel pharmaceuticals and ultrafine particles are being drawn upon for managing ENM based on the similar diffusion behavior and properties they exhibit.[39,43,44]

METHODS

A search of articles referencing occupational exposure controls for nanomaterials were compiled through literature database searches. Databases searched included Scholars Portal, Scopus, and PubMed. Key words were searched using Boolean logic and included nanoparticles, exposure control, and control banding. Results were limited from 2003–2014 (March) inclusive. In addition to academic literature searches, reports from international organizations on the EHS concerns and management of nanomaterials were reviewed for context and application. Articles meeting the search criteria were reviewed for applicability to the subject and contributed to the development of a management model. Based on these findings, an integrative model for managing ENM exposures was synthesized.

RESULTS

Proposed Framework

The limited applicability of regulatory systems in mandating ENM controls has created an environment for innovative solutions to mitigate potential health concerns. The proposed Nanomaterial Occupational Exposure Management (NOEM) Model suggests three activities to implement as part of an exposure management program – Risk Assessment, Exposure Control, and Exposure Monitoring (Figure 1).

Based on evidence from academic research, two independently piloted and peer-reviewed resources for managing occupational exposures were integrated to address the three components of the NOEM Model. The first and second components of the model- Risk Assessment and Exposure Control, use the semi-quantitative *Control Banding* (*CB) Nanotool* developed by Paik[45] and revised by Zalk et al.[42] This tool calculates a risk level based on the severity and probability of a specific exposure, which coincides with a control band to guide occupational exposure mitigation strategies. The third component, Exposure Monitoring, applies the categorical exposure monitoring standard proposed by the German Institute for Occupational Safety and Health (IFA) which was later adopted by the Dutch Social Economic Council as *Nano Reference Values (NRVs)*, to act in lieu of traditional occupational exposure limits for nanomaterials. Through the use of *NRVs* as a monitoring standard, the effectiveness of control measure can be verified while also providing feedback to drive continuous improvement and re-assessment of the exposure risk.

The NOEM model, through the integration of two prescriptive resources, becomes a pragmatic and iterative process for industry to adopt in order to manage occupational exposure risks from ENM. In light of limited regulatory oversight, the NOEM model can meet the needs of industry to manage occupational risks as per due diligence requirements, while still providing flexibility to incorporate evolving technologies for applications and controls.

Resources for the NOEM Model

The assessment of an exposure risk is important for establishing the extent and urgency for implementing control measures. When risk level quantification is based on relevant parameters, the properties with the greatest contributors to the exposure risk can be identified. This knowledge can assist with the development of control measures that are both effective and an efficient use of resources. The *CB Nanotool*[42,45] calculates a risk level based on the product of a severity and probability score, each of which incorporates weighted parameters. The severity rating incorporates 15 factors supported by literature as key determinants of toxicity,[17] 70% of which are attributed to the nanomaterial characteristics, with the remaining 30% from the parent or bulk material.[42,45] The probability score is determined by five factors that characterize the exposure potential. Each of the factors, in both the severity and probability, has a scale of options that correspond to point values. Uncertainty in any factor is addressed by assigning a hazard rating of 75% the maximum point value, which represents a precautionary level that avoided mandating an excessive protection level.[42,45] Risk ratings are placed into exclusive ranges that correspond to a band in the conventional four control banding categories.

Since traditional risk assessment practices are unable to guide exposure mitigation,[46] precautionary and pragmatic control schemes such as control banding have been supported as an effective preliminary risk management approach.[24,30,43,45,46] The strength of control banding lies in that the limited information on ENM toxicity can be offset by the designing protective control measures based on the known data.[24,41,42,44] Various control banding tools that have been developed that have a specific focus on nanomaterials. A review by Brouwer[30] compares and contrasts the components of control banding system such as the *CB Nanotool*, the Precautionary Martix, ANSES guidance, the Stoffenmanager Nano, Guidance from Dutch Social Partners, and lastly, the Nanosafer. The *CB Nanotool* was selected as the control banding tool for the NOEM model in part due to its formulaic approach in determining a protective, risk-based control banding category for a given scenario. In a pilot of the *CB Nanotool* in industry, the recommended control bands were found to be consistent with professional recommendations from industrial hygienists based on the risk level of the studied processes.[42] The weighted and non-binary approach of the CB Nanotool offers the end-users insight for conducting a sensitivity analysis to gain a greater understanding of the factors contributing to the risk level of a process. As a risk assessment tool, the CB Nanotool can be applied at stages before exposures occur, such as when conducting planning and pre-operation assessments for the introduction of new technology or processes involving ENMs. Additionally, the CB Nanotool is not restrictive to situations where only a comprehensive understanding of the ENM of inquiry is available, as it provides a factor for addressing uncertainty that does not assume the worse-case risk level. This is valuable for assessing and controlling risks associated with exposure scenarios such as those occurring in research settings, which may be temporary or highly variable as applications change.(47) With traditional exposure management rooted in industrial hygiene monitoring for the establishment of controls and their effectiveness, temporary scenarios and uncertainty in the knowledge of ENM properties make the control banding resources such as the *CB Nanotool* an appropriate central component of an ENM exposure management program.(48)

Given that there are very few nano-specific OELs due to debate over suitable metrics, the quantitative monitoring of ENM exposures becomes a challenging exercise for constructive interpretation.(5,28) The NOEM model addresses this by integrating the categorical exposure levels developed by the IFA as the standard for the Exposure Monitoring portion of the model. Based on benchmarking, the IFA identified four categorical groups based on the parameters of size, form, biopersistence, and density to evaluate exposures of ENMs against.(36,49,50) The application of a categorical-based exposure standard for ENM groups with similar properties, or modes of action, allows for an adaptive management approach that can keep pace with ENM development.(34,50) This broad applicability allows for an environment that fosters nanotechnology innovation while managing risks.(8,23,34,36) A categorical approach also has benefits in more efficiently using resources for research purposes, reducing costs and animal usage in testing, and increased sample size for the effects of a mode of action.(4,23)

The Netherlands adapted the IFA's guidance structure into *NRVs* and implemented them in 2012 based on the recommendation of the Dutch Social Economic Council, an advisory group to the Dutch government and parliament.(49) The implementation of *NRVs* as an exposure standard was piloted in a study of Dutch industry partners(49) where industry and regulators accepted *NRVs* given that material concentrations were found to be below the prescribed exposure levels when conventional control strategies were implemented.(34,36,49)

DISCUSSION

Integration of NOEM Model

Quantitative risk assessment frameworks often serve as the basis for regulatory policies and associated enforcement standards.(25) The NOEM model takes a risk-based approach that integrates current research to create a model for managing exposures (Figure 2). This cyclical process completed by the inclusion of an exposure monitoring standard (Figure 2)

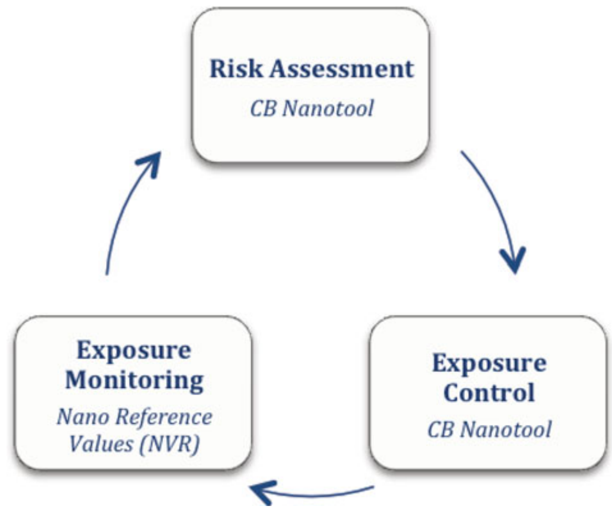

FIGURE 1. NOEM Model.

supports the use of control banding as a valid central method for managing ENM exposures that have limited quantitative methods and standards (i.e., occupational exposure limits) on which to base an exposure control program.(47,48) The need for a pragmatic model, such as the NOEM, for managing ENM exposures exists in light of inconsistent perceptions on the potential risk,(9) and the absence of risk governance measures.(3,51) The risk assessment process in the *CB Nanotool* provides risk-based guidance for implementing control banding to mitigate exposures, while *NRVs* provide a standard to assess control measures and ultimately verify the effectiveness of the assigned control band. The NOEM Model can aid in risk management, an integral part of a health and safety management system, as it is an iterative process much like the Plan-Do-Check-Act-Verify cycle.(13,23,24,43)

To complete the risk assessment portion of the NOEM model, the properties of the material, in addition to the circumstances under which the exposure is occurring, must be amassed. The completion of the severity assessment in this process provides an account of the hazardous properties intrinsic to ENMs with an emphasis on the health implications. To strengthen the risk assessment process, engaging a multidisciplinary group would provide insight on the variability of hazards throughout a process where ENM are utilized. Furthermore, a process review is beneficial in identifying the safety concerns that may arise with maintenance activities, critical emergency situations (e.g., fires or loss of containment),(52) and waste, environmental, and potential public health concerns.(53)

Ideally, the hazard information should come from standardized communication tools such as Safety Data Sheets (SDS) as advocated in the *Stoffenmanager Nano* tool.(30) Currently, SDSs are inconsistent across the variety of ENMs due to incomplete data sets and ongoing debate over standard parameters of exposure.(54,55) These issues limit the ability of SDSs to provide strategic direction required for risk management.(42,54,55) Similarly, the SDSs of parent material fails

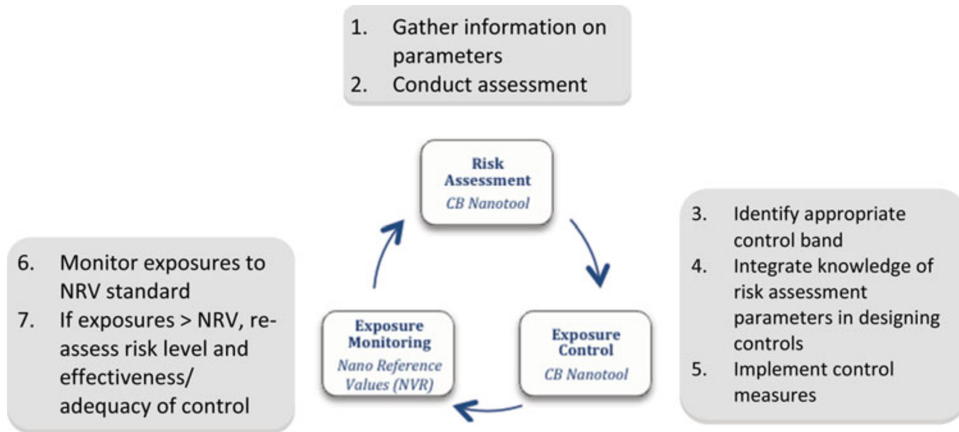

FIGURE 2. NOEM Model with activity integration.

to account for the unique hazards presented by the nano-scale of ENMs. In accounting for the hazardous properties of ENMs, the *CB Nanotool* takes the approach that the health outcomes associated with ENMs differs from parent compounds,[42] while still respecting that characteristics of parent compounds can be influential at the nano-scale.[29] Thus, in the interim, until consensus has been reached on documenting hazardous properties which can be reflected in standardized SDSs, academic research must be relied upon to collect the information called upon in the severity analysis of the risk assessment. Ideally, the relevant scientific information on a nanomaterial should be documented in hazard communication tools along with the associated uncertainties as a method of prioritizing which developments should be closely monitored in document reviews. This strategy would communicate the limitations of knowledge and serve as way to justify the implementation of protective measures and activities necessitated by due diligence clauses in leading occupational health and safety regulations.

The *CB Nanotool* further works towards understanding the risk of an ENM exposure through the weighting and scoring of parameters. Based on both the severity and probability aspects used in determining the risk level, the data that is compiled through the risk assessment process supplies information that can enhance how control measures are designed and implemented.[29] The prioritization of variables in the probability assessment is particularly beneficial as it considers the factors that influence exposure potential, knowledge of which can contribute to the efficient design of control measures.[42] As the parameters affecting ENM toxicity and occupational exposures are better understood, the strategies to mitigate exposures will have to adjust beyond the basic guidance of control bands.[56] The variety of mitigation measures encompassed in each control band allows users a high degree of flexibility while guiding them in a protective direction to control exposures.[24,42] In a pilot of the *CB Nanotool* in industry, the recommended control band outcomes were found to be consistent with professional recommendations from industrial hygienists.[42] Additionally, as ENM exposures become more common, the verification of control banding assignments is supported where industrial hygiene monitoring has been used to verify control measures.[47] Therefore, the *CB Nanotool* is not only a resource for Risk Assessment but also useful in guiding Exposure Controls in the NOEM Model.

Although control banding is accepted as a method for establishing controls for ENM exposures, the verification of effectiveness is still necessary to satisfy the iterative nature of the risk assessment process.[5,23,28] Categorical occupational exposure limits, such as the outlined in the *NRVs*, serve as the quantitative link in the iterative risk management process by being a means of calibrating or validating a risk management model.[23] Figure 3 depicts the NRVs as mass concentrations for four particle sizes in comparison to their associated ACGIH TLVs. For the size range of 1–100 nm, the NRVs fall below the ACGIH TLV value of their parent compound with the exception of lead. Where *NRVs or the OELs of parent compounds* are exceeded, control measure should be evaluated for effectiveness, or the risk assessment and assignment of control bands re-evaluated to ensure they are accurately accounting for parameters. *NRVs*, as action levels, are intended to be protective in exposure management as a standard for evaluating exposure levels against.[57] Additionally, since *NRVs* are preliminary levels, should traditional health-based OELs be established, supported, and verified for ENMs through meeting established quantitative risk assessment standards, the *NRVs* would be superseded as basis for evaluating control strategies.[57] This was also the consensus reached by Dutch Social Economic Council on the implementation of *NRVs*.[49,50]

Barriers to Implementation

The quantification of ENM exposure levels can be costly, time-consuming, and require highly specialized equipment and personnel to execute.[5,30,47,58] Numerous authors and organizations have recommended sampling strategies for

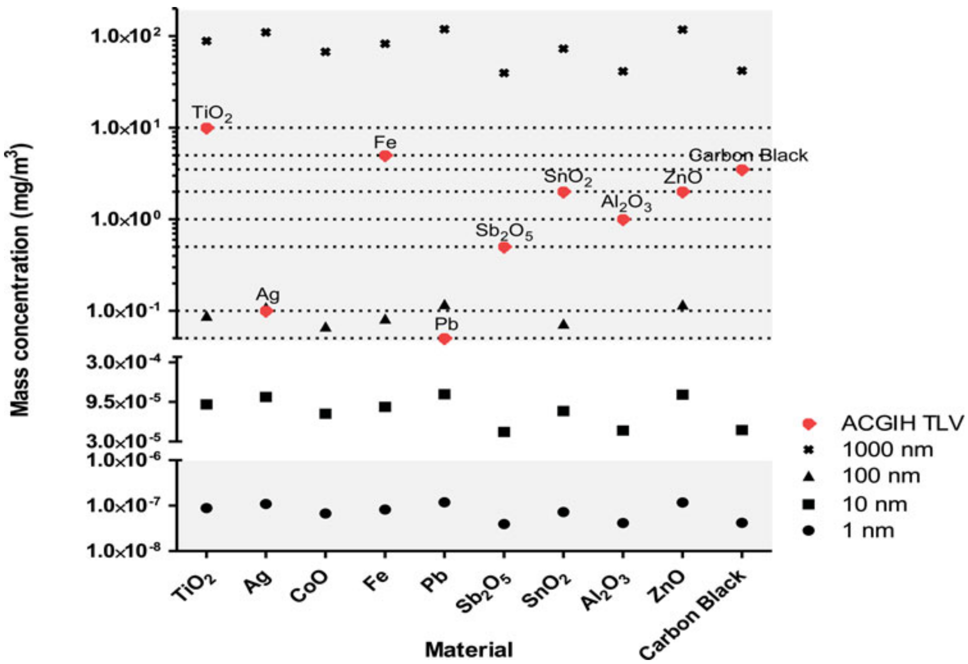

FIGURE 3. NRVs converted to mass concentrations at four particle sizes with associated ACGIH TLV values

ENMs that incorporate several methods of measurement, but all recognize the limitations of current methodologies in accounting for potential background interferences while collecting a representative sample of a workers exposure.(5,11,20,24,28,30,31,34,43,56,58,59,60) A challenge inherent in any management model that includes a quantitative evaluation component is the identification and assessment of environmental interferences.(53,59) As research develops on measurement aspects of ENM exposures, improvements are made in the accessibility of technology for the assessment differentiation of background interferences.(14,53,59,61) Characterizing a process and its surroundings for sources of interferences, the ENM characteristics and the existing sample methods, even with their limitations, are currently the leading methods to identify and account for interferences while implementing an assessment strategy.(1,58)

Although challenges exist for the technology and methodology, the inclusion of exposure monitoring within the NOEM Model encourages quantitative assessments methodologies to be developed. Such standardized methods for the monitoring and analytical interpretation of results would provide consistency in implementing of frameworks, such as NOEM, for controlling exposures.(20,61) In addition, promoting the development of exposure monitoring standards and technologies builds the capacity to estimate exposures and ultimately strengthen risk management practices.(1,5,59,61) Support for monitoring exposure levels also contributed towards ensuring the responsible advancement of nanotechnology and ENM applications by employers and innovators.(1,11,23)

The NOEM Model, as an ENM exposure management framework, should be incorporated into proactive occupational risk management systems and program planning.(43,51,62) Although the control banding component of the NOEM model has limitations in the ability to assess all the hazards of a process where ENMs are present, it, and other control banding tools, provide specific guidance that cannot be afforded by tools such as life-cycle assessments. For the hazard characterization and risk assessment of situations outside of what is covered through the NOEM model, further resources should be appended to process which incorporate the relevant experienced parties (e.g., fire and explosion hazards, environmental release, public health implications).(52)

Industry implementation of a voluntary management model can be inconsistent given the inherent conflict of interest in the self-imposition of control measures, the uncertainty of ENM risk data, and perceptions that industry understands the associated risk of ENMs.(9,62) The NOEM Model would benefit from its promotion as a progressive interim alternative to a zero-exposure regulatory model, which could restrict innovation and development.(8,34,50)

Further Research Needs

The rapid development of nanotechnology and diverse ENM applications will continue to create challenges for occupational risk management.(5,11) To facilitate an environment where protective measures can be applied and carried beyond the early stages of ENM exploration, standardization initiatives in the areas of terminology, classification systems, toxicological parameters, and mechanisms of action must continue to be supported. As the basis for decisions on occupational management strategies, toxicological and exposure parameters should also continue to be explored.(20,23,46) Once consensus on key parameters and the scope of ENM toxicological research is reached, hazard communication tools such as SDSs, and the quantitative evaluation standards (NRVs) should be re-evaluated as resources for risk management.[63]

As developments in exposure parameters progress, metrological research for the quantification of occupational exposures should be investigated to generate cost-effective and efficient assessment methods for ENM. The need for such advancements would strengthen management models.

CONCLUSION

In light of the uncertainties in the health risks associated with ENM exposures, the NOEM Model is a risk-based approach to managing potential health risks as currently identified. It is intended to serve as an iterative guide in ENM generation and application to address occupational exposure concerns in manufacturing and industrial settings. The NOEM Model is applicable to a range of ENMs and exposure scenarios by bridging best practices from traditional control mechanisms with emerging research. The pragmatic and protective approach employed to managing occupational exposure potential provides justifiable control measures based on a hazard's level of risk. This model can be incorporated into existing risk management strategies to act as in interim framework until applicable regulatory systems are imposed or recommended.

REFERENCES

1. **Abbott, L.C., and A.D. Maynard**: Exposure assessment approaches for engineered nanomaterials. *Risk Anal. 30*(*11*):1634–1644 (2010).
2. **Becker, H.**, **F. Herzberg**, **A. Schulte**, **and M. Kolossa-Gehring**: The carcinogenic potential of nanomaterials, their release from products and options for regulating them. *Int. J. Hyg. Environ. Health 214*(*3*):231–238 (2011).
3. **Engeman, C.D.**, **L. Baumgartner**, **B.M. Carr**, **et al.:** The hierarchy of environmental health and safety practices in the U.S. nanotechnology workplace. *J. Occup. Environ. Hyg. 10*(*9*):487–495 (2013).
4. **OECD**: *Report of the OECD Workshop on the Safety of Manufactured Nanomaterials Building Co-operation, Co-ordination and Communication*. Organisation for Economic Co-operation and Development, Washington, 2006.
5. **Ramachandran, G.**, **M. Ostraat**, **D.E. Evans**, **et al.:** A strategy for assessing workplace exposures to nanomaterials. *J. Occup. Environ. Hyg. 8*(*11*):673–685 (2011).
6. **The Royal Society**: *Nanoscience and Nanotechnologies: Opportunities and Uncertainties*. London, England: Science Policy Section, The Royal Society, 2004.
7. **Ostiguy, C.**: *Engineered Nanoparticles: Current Knowledge about OHS Risks and Prevention Measures*. Queébec, Canada: IRSST, 2010.
8. **Council of Canadian Academies**: *Small is Different a Scientific Perspective on the Regulatory Challenges of the Nanoscale*. Ottawa, Ontario: Council of Canadian Academies/ Conseil des académies canadiennes, 2008.
9. **Engeman, C.D.**, **L. Baumgartner**, **B.M. Carr**, **et al.:** Governance implications of nanomaterials companies' inconsistent risk perceptions and safety practices. *J. Nanopart. Res. 14*(*3*):1 (2012).
10. **Card, J.W.**, **D.C. Zeldin**, **J.C. Bonner**, **and E.R. Nestmann**: Pulmonary applications and toxicity of engineered nanoparticles. *Am. J. Physiol. Lung Cell. Molec. Physiol. 295*(*3*):L400–411 (2008).
11. **Murashov, V.**, **P. Schulte**, **and J. Howard**: Progression of occupational risk management with advances in nanomaterials. *J. Occup. Environ. Hyg. 9*(*1*):D12–D22 (2012).
12. **Hallock, M.F.**, **P. Greenley**, **L. DiBerardinis, and D. Kallin**: Potential risks of nanomaterials and how to safely handle materials of uncertain toxicity. *J. Chem. Health Safety 16*(*1*):16–23 (2009).
13. **Grieger, K.D.**, **A. Baun**, **and R. Owen**: Redefining risk research priorities for nanomaterials. *J. Nanopart. Res. 12*(*2*):383–392 (2010).
14. **Brouwer, D.**, **M. Berges**, **M.A. Virji**, **et al.:** Harmonization of measurement strategies for exposure to manufactured nano-objects; report of a workshop. *Ann. Occup. Hyg. 56*(*1*):1–9 (2012).
15. **Oberdörster, G.**: Pulmonary effects of inhaled ultrafine particles. *Int. Arch. Occup. Environ. 74*(*1*):1 (2001).
16. **Donaldson, K.**, **X.Y. Li, and W. MacNee**: Ultrafine (nanometre) particle mediated lung injury. *J. Aerosol Sci. 29*(*5*):553–560 (1998).
17. **Oberdörster, G.**, **D. Lai**, **S. Olin**, **et al.:** ILSI Research Foundation/Risk Science Institute Nanomaterial Toxicity Screening Working Group. Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy. *Part. Fibre Toxicol. 2*(*1*):8–8 (2005).
18. **Ostiguy, C.**, **B. Soucy**, **G. Lapointe**, **C. Woods**, **L. Menard, and M. Trottier**: *Health Effects of Nanoparticles: Second Edition. (No. R-589)*. Montreal, Canada: Institut de Recherche Robert-Sauve en Sante et en Securite du Travail (IRSST), 2008.
19. **ISO**: *ISO/TR 12885:2008 Nanotechnologies -Health and Safety Practices in Occupational Settings Relevant to Nanotechnologies*. (*No*. ISO/TR 12885:2008). Switzerland: ISO, 2008.
20. **Brouwer, D.**: Exposure to manufactured nanoparticles in different workplaces. *Toxicology 269*(*2–3*):120–127 (2010).
21. **BSI**: *Guide to Safe Handling and Disposal of Manufactured Nanomaterials*. (No. PD6699–2). British Standards Institute, PD6699–2, 2007.
22. **Gordon, S.C.**, **J. West**, **J.H. Butala**, **et al.:** Workshop report: Strategies for setting occupational exposure limits for engineered nanomaterials. *Regul. Toxicol. Pharmacol. 68*(*3*):305–311 (2014).
23. **Kuempel, E.D.**, **V. Castranova**, **C.L. Geraci, and P.A. Schulte**: Development of risk-based nanomaterial groups for occupational exposure control. *J. Nanopart. Res. 14*(*9*):1–15 (2012).
24. **Maynard, A.D.**: Nanotechnology: The next big thing, or much ado about nothing? *Ann. Occup. Hyg. 51*(*1*):1–12 (2007).
25. **Myers, M.L.**: Anticipation of risks and benefits of emerging technologies: A prospective analysis method. *Hum. Ecol. Risk Assess. Int. J. 13*(*5*):1042–1052 (2007).
26. **NIOSH**: *Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide*. Cincinnati, Ohio: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publ. Num. 2011–160:1–119 (2011).
27. **NIOSH**: *Current Intelligence Bulletin 65: Occupational Exposure to Carbon Nanotubes and Nanofibers*. Cincinnati, Ohio: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publ. No. 2013–145:1–156 (2013).
28. **Schulte, P.A.**, **V. Murashov**, **R. Zumwalde**, **E.D. Kuempel, and C.L. Geraci**: Occupational exposure limits for nanomaterials: State of the art. *J. Nanopart. Res. 12*(*6*):1971–1987 (2010).
29. **Warheit, D.B.**, **C.M. Sayes**, **K.L. Reed, and K.A. Swain**: Health effects related to nanoparticle exposures: Environmental, health and safety considerations for assessing hazards and risks. *Pharmacol. Therapeut. 120*(*1*):35–42 (2008).
30. **Brouwer, D.H.**: Control banding approaches for nanomaterials. *Ann. Occup. Hyg. 56*(*5*):506–514 (2012).
31. **Methner, M.**, **L. Hodson, and C. Geraci**: Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials—part A. *J. Occup. Environ. Hyg. 7*(*3*):127–132 (2009a).

32. **Rushton, E.K.**, **J. Finkelstein**, **G. Oberdörster**, **et al.:** Concept of assessing nanoparticle hazards considering nanoparticle dosemetric and chemical/biological response metrics. *J. Toxicol. Environ. Health Part A 73*(*5*):445–461 (2010).
33. **ISO**.: *ISO/TR 12802 nanotechnologies - model taxonomic framework for use in developing vocabularies - core concepts*. (*No*. ISO/TR 12802:2010(E)). Switzerland: ISO.(2010)
34. **van Broekhuizen, P., and B. Dorbeck-Jung**: Exposure limit values for nanomaterials—Capacity and willingness of users to apply a precautionary approach. *J. Occup. Environ. Hyg. 10*(*1*):46–53 (2013).
35. **Duffin, R.**, **C.L. Tran**, **A. Clouter**, **et al.:** The importance of surface area and specific reactivity in the acute pulmonary inflammatory response to particles. *Ann. Occup. Hyg. 46*(*Suppl. 1*):242–245 (2002).
36. **van Broekhuizen, P.**, **F. van Broekhuizen**, **R. Cornelissen, and L. Reijnders**: Workplace exposure to nanoparticles and the application of provisional nanoreference values in times of uncertain risks. *J. Nanopart. Res. 14*(*4*):1–25 (2012a).
37. **Morimoto, Y.**, **N. Kobayashi**, **N. Shinohara**, **T. Myojo**, **I. Tanaka, and J. Nakanishi**: Hazard assessments of manufactured nanomaterials. *J. Occup. Health 52*(*6*):325–334 (2010).
38. **Brooke, I.**: A UK scheme to help small firms control health risks from chemicals: toxicological considerations. *Ann. Occup. Hyg. 42*(*6*):377–390 (1998).
39. **Guest, I.**: The chemical industries association guidance on allocating occupatioal exposure bands. *Ann. Occup. Hyg. 42*(*6*):407–411 (1998).
40. **Russell, R.M.**, **S.C. Maidment**, **I. Brooke, and M.D. Topping**: An introduction to a UK scheme to help small firms control health risks from chemicals. *Ann. Occup. Hyg. 42*(*6*):367–376 (1998).
41. **Maidment, S.C.**: Occupational hygiene considerations in the development of a structured approach to select chemical control strategies. *Ann. Occup. Hyg. 42*(*6*):391–400 (1998).
42. **Zalk, D.M.**, **S.Y. Paik, and P. Swuste**: Evaluating the control banding nanotool: A qualitative risk assessment method for controlling nanoparticle exposures. *J. Nanopart. Res. Interdiscipl. Forum Nanoscale Sci. Technol. 11*(*7*):1685 (2009).
43. **Schulte, P.**, **C. Geraci**, **R. Zumwalde**, **M. Hoover, and E. Kuempel**: Occupational risk management of engineered nanoparticles. *J. Occup. Environ. Hyg. 5*(*4*):239–249 (2008b).
44. **Zalk, D.M., and D.I. Nelson**: History and evolution of control banding: A review. *J. Occup. Environ. Hyg. 5*(*5*):330–346 (2008).
45. **Paik, S.Y.**, **D.M. Zalk, and P. Swuste**: Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. *Ann. Occup. Hyg. 52*(*6*):419–428 (2008).
46. **Savolainen, K.**, **L. Pylkkänen**, **H. Norppa**, **et al.:** Nanotechnologies, engineered nanomaterials and occupational health and safety – A review. *Safety Sci. 48*(*8*):957–963 (2010).
47. **Casuccio, G.**, **R. Ogle**, **K. Bunker, et al.:** Worker and Environmental Assessment of Potential Unbound Engineered Nanoparticle Releases-Phase III Final Report: Validation of Preliminary Control Band Assignments. RJ Lee Goup Inc & E.O. Lawrence Berkeley National Laboratory, 2010. Available at http://www2.lbl.gov/ehs/esg/Reports/assets/Phase%20III%20Final%20Report2010.pdf
48. **Casuccio, G.**, **R. Ogle**, **L. Wahl, and R. Pauer**: Worker and Environmental Assessment of Potential Unbound Engineered Nanoparticle Releases- Phase II Final Report: Preliminary Control Band Development. RJ Lee Goup Inc & E.O. Lawrence Berkeley National Laboratory, 2009. Available at http://www2.lbl.gov/ehs/esg/Reports/assets/Phase%20II%20Final%20Report2009.pdf
49. **IFA**: "Criteria for assessment of the effectiveness of protective measures. institut fur arbeitsschutz der deutschen gesetzlichen unfallversicherung," 2009. Available at http://www.dguv.de/ifa/Fachinfos/Nanopartikel-am-Arbeitsplatz/Beurteilung-von-Schutzma%C3%9Fnahmen/index-2.jsp (Retrieved March 6, 2014).
50. **Van Broekhuizen, P.**, **W. Van Veelen**, **W. Streekstra**, **P. Schulte, and L. Reijnders**: Exposure limits for nanoparticles: Report of an international workshop on nano reference values. *Ann. Occup. Hyg. 56*(*5*):515–524 (2012b).
51. **Helland, A.**, **H. Kastenholz**, **A. Thidell**, **P. Arnfalk, and K. Deppert**: Special activities (research centres, institutes etc.), Internationella miljöinstitutet. Nanoparticulate materials and regulatory policy in Europe: An analysis of stakeholder perspectives. *J. Nanopart. Res. 8*(*5*):709–719 (2006).
52. **Vignes, A.**, **F. Muñoz**, **J. Bouillard**, **et al.:** Risk assessment of the ignitability and explosivity of aluminum nanopowders. *Process Safety Environ. Protect. 90*(*4*):304–310 (2012). Available at http://dx.doi.org.proxy.bib.uottawa.ca/10.1016/j.psep.2011.09.008
53. **Casuccio, G.**, **R. Ogle, and L. Wahl**: Environmental Monitoring Plan for Unbound Engineered Nanoparticles. RJ Lee Goup Inc & E.O. Lawrence Berkeley National Laboratory, 2011. Available at http://www2.lbl.gov/ehs/esg/Reports/assets/Phase%20IV%20EnvNanoMonitoringPlan10-5-11.pdf
54. **Eastlake, A.**, **L. Hodson**, **C. Geraci, and C. Crawford**: A critical evaluation of material safety data sheets (MSDSs) for engineered nanomaterials. *J. Chem. Health Safety 19*(*5*):1–8 (2012).
55. **Lee, J.H.**, **W.K. Kuk**, **M. Kwon**, **J.H. Lee**, **K.S. Lee, and I.J. Yu**: Evaluation of information in nanomaterial safety data sheets and development of international standard for guidance on preparation of nanomaterial safety data sheets. *Nanotoxicology 7*(*3*):338–345 (2013).
56. **Schulte, P.A.**, **D. Trout**, **R.D. Zumwalde**, **et al.:** Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: State of the science. *J. Occup. Environ. Med. 50*(*5*):517–526 (2008a).
57. **Social and Economic Council of The Netherlands (SER)**: *Provisional Nano Reference Values for Engineered Nanomaterials: Advisory Report. (No. 12/01)*. Den Haag, The Netherlands, 2012. Available at http://www.ser.nl/~/media/Files/Internet/Talen/Engels/2012/2012_01/2012_01.ashx
58. **Songmene, V.**, **J. Masounave**, **M. Viens**, **S. Hallé, and F. Morency**: "Procedure for measuring and controlling manufactured nanoparticles," 2010. Available at http://www.irsst.qc.ca/en/-project-procedure-for-measuring-and-controlling-manufactured-nanoparticles-0099-7860.html (accessed October 25, 2013).
59. **Methner, M.**, **L. Hodson**, **A. Dames, and C. Geraci**: Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials—part B: Results from 12 field studies. *J. Occup. Environ. Hyg. 7*(*3*):163–176 (2009b).
60. **Schulte, P.A.**, **M.K. Schubauer-Berigan**, **C. Mayweather**, **C.L. Geraci**, **R. Zumwalde, and J.L. McKernan**: Issues in the development of epidemiologic studies of workers exposed to engineered nanoparticles. *J. Occup. Environ. Med. 51*(*3*):323–335 (2009).
61. **Methner, M.**, **C. Beaucham**, **C. Crawford**, **L. Hodson, and C. Geraci**: Field application of the nanoparticle emission assessment technique (NEAT): Task-based air monitoring during the processing of engineered nanomaterials (ENM) at four facilities. *J. Occup. Environ. Hyg. 9*(*9*):543–555 (2012).
62. **Helland, A.**, **M. Scheringer**, **M. Siegrist**, **H.G. Kastenholz**, **A. Wiek, and R.W. Scholz**: Risk assessment of engineered nanomaterials: A survey of industrial approaches. *Environ. Sci. Technol. 42*(*2*):640–646 (2008).
63. **ISO**: *ISO/TR 13329:2012 - Nanomaterials - Preparation of Material Safety Data Sheet (MSDS)*, 2012. Switzerland. Available at http://www.iso.org/iso/catalogue_detail.htm?csnumber=53705