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Critical Research Needs to Address Occupational Safety and Health of Nanomaterial Workers

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ABSTRACT. Conceptually, the initial phase of nanomaterial occupational safety and health research is now largely completed and the next phase targeting more refined research is starting. The pending question is what is the critical research that should be conducted to move the field forward and advance worker protection. Research is needed to further understand toxic effects of nanomaterials. There is also need for more exposure data, and for data on the prevalence of the use of controls to prevent worker exposures. One growing area that needs attention is determination of ENM exposure in additive manufacturing. Overall, for the nanomaterial workforce enough time has now passed to consider and implement more rigorous longitudinal epidemiological studies of various groups of workers. Additionally, special attention needs to be continued for investigation of hazard risk and control of exposure to high aspect ratio nanomaterials. Most importantly, there is need for continued refinement of strategies to group nanomaterials and develop categorical risk management guidance.

Key words: *nanotechnology, toxicology, carbon nanotubes.*

Introduction

Engineered nanomaterials (ENM) have been commercially produced for roughly 20 years. Initially there were concerns that ENMs could be hazardous to people and the environment. The initial health concerns arose from what is known about hazards and exposures to ultrafine particles both in industry and in air pollution. Subsequent findings have not lessened those concerns. Rather, the studies to date have provided the type of information that, while not conclusive, promotes the need for further research (Savolainen et al 2010, Schulte et al 2016). The hopeful aspect is that based on what has been learned it is now possible to make some refined determinations of what are critical occupational safety and health research needs for the near future.

The initial critical research needs for addressing the safety and health of nanomaterial workers have been considered early in the 2000's (HSE, 2004: Royal Society/ Academy Engineering 2004; Maynard et al 2006, NIOSH 2009). During the first two decades findings such as, pulmonary inflammation, fibrosis, and cancer in animals exposed to CNTs have raised some of the initial concerns that workers could be at risk of various adverse pulmonary effect (Shvedova et al 2005, Sargent et al 2014; Suzui et al 2016). Cardiovascular, hepatic, and renal effects also have been associated with exposure to some nanomaterials in rodents (Li et al 2007; Weldon et al 2016).

Hazard Identification

The early toxicological research could be described as "range finding"—evaluating the potential toxicity of ENM in the context of existing respiratory hazards. Consequently much of the initial hazard research was aimed at identifying early signals of toxicity, basic mechanisms, and capabilities of ENM in biological systems. Due to the limitations in testing all ENMs individually more refined and targeted research is needed to build on existing knowledge to develop evidence-based occupational safety and health guidance (Kuempel et al 2012). A critical evaluation of the state of nanotoxicology studies suggests areas for improving data in the future including better and more comprehensive characterization of ENM and more clearly defined toxicology studies (Krug 2014). A key future need is the systematic evaluation of the toxicity of a range of particle types and sizes to obtain a clearer picture of the properties that influence the toxicity of ENMs especially for materials widely used in commerce (e.g. "OECD11") (OECD 2016). That initial phase of the hazard research is now largely completed and the next phase targeting more refined research is starting.

Toxicological studies that are most relevant to assessing occupational safety and health hazards utilize aerosols that are representative of the kind of aerosols that exist in the work place (e.g. agglomerates). For example, when aerosols are generated in the workplace, they often agglomerate although the extent of agglomeration or dispersion depends on the properties of the materials and the tasks involved. What is in the breathing zone of works should be what is used in animal studies with the additional consideration and characterization of the inhalable and respirable particle sizes in the rat or mouse.

It is also of importance is to conduct toxicological studies of the smallest materials that result from applying kinetic energy to nanomaterials embedded in matrices. Generally, early research has shown that what is released in sanding, grinding, and cutting is not free nanomaterials, but large clumped materials (Heitbrink and Lo 2016; Froggett et al 2014). Aerosols from processes that generate the "smallest" of these clumped materials should be tested toxicologically. This will require developments in aerosol generation systems for toxicity testing of ENMs.

Exposure Assessment

Another important research need is to fill the gap in the availability of task-based exposure data which is often missing or limited in published exposure data. Additionally, attention to background exposure to incidental nanomaterials is often lacking. While focus has been on health effects of ENMs, the more appropriate occupational health view would be to focus on all particles in work place atmospheres and provide comprehensive exposure and risk appraisals including interactions among exposure materials and their biological behavior.

Exposure characterization is also needed for new areas of advanced manufacturing. There are many areas of advanced manufacturing where workers may be exposed to nanomalmaterials (NSTC 2013). One area that has received initial attention is "additive manufacturing". Additive manufacturing of metal objects often uses sub-micron powders (nanoparticles) as a base material. Common metals include steels, as well as nickel-and titanium-based alloys (Gu et al. 2012; Murr et al. 2012). Both for metallic and non-metallic products, ENMs are increasingly being explored as additives. Materials such as carbon nanotubes are primarily exploited for their effects on materials strength. Other ENM additives, such as silver, are sought for their effects on the process itself (Ivanova et al. 2013).

The additive manufacturing market is expected to reach over $5 billion before 2020 (Campbell and Ivanova 2013). These techniques are likely to see use in aerospace and automotive manufacturing, medical device manufacturing, and several other sectors (Campbell et al. 2011; Conner et al. 2014). Consequently, the work force that could potentially face exposure is quite large. Despite this, there is currently insufficient exposure research. While some publications explore the potential nanoparticle release during fused filament fabrication, (Azimi et al. 2016; Kim et al. 2015) industrial scale techniques such as selected laser sintering have not been assessed. Also neglected is the question of exposure during maintenance operations, such as cleaning. Characterization of these tasks would better enable application of risk assessment and management tasks that have been and are continuing to be developed for ENMs.

Risk Assessment

Another high priority research area is the need to conduct studies to address some of the uncertainties in risk assessments. These studies might include epigenetic and other mechanistic pathways that would inform selection of uncertainty factors. In risk assessment there is a need to address the concerns about grouping approaches as described by Arts et al 2014 who found that most grouping schemes utilize: ENM material properties and biophysical interactions; specific types of uses and exposures; uptake and kinetics; and possible early and apical biological effects. However, none fully take into account all of these aspects and the concern is that risk assessments based on such material properties over-or under-estimate hazards or fail to recognize relevant risks at all. This conclusion may need refining because it does not take a public health view which entails making tradeoffs between certainty and actions. Nonetheless there is a need for research to support categorical approaches and development of group risk assessments (Kuempel et al 2012).

There have been few epidemiological studies of nanomaterial and those that have been published generally suffered from minimal data on weak exposure assessment (Liou et al 2015). There is a need for longitudinal study designs and this may require forming cohorts from various companies. The issues in conducting longitudinal studies have been identified and include sample size, exposure homogenies, cost and time (Riediker et al 2012; Schulte et al 2009). In recent years cross-sectional studies using nonspecific biomarkers have been conducted (Liou et al, 2015). Further research is needed to establish potentially useful biomarkers for studies of nanomaterial workers.

Risk Management

Risk management is another area where there are critical research needs. These needs focus on knowing how well risk management efforts are protecting workers and to what extent recommended approaches are being used (Schulte et al 2016). Most of the risk management guidance follows the well-established and validated hierarchy of controls. What is not known is how well the guidance is applied in various work settings and where there may be tasks and jobs where application of controls is problematic. To assess the application and effectiveness of risk management guidance there is a need for studies of workplaces. These might be by sector, product, tasks, along the value chain or life cycle, but such studies will be difficult and costly to conduct, and part of the research might be to find creative ways to assess the application of risk management approaches. The assessment of the extent and effectiveness of application of risk management guidance is a difficult issue as it generally entails field assessments and on-site studies of control approaches for specific tasks. Some of these on-site studies might be supplemented by laboratory investigations of controls. Research on risk management application and effectiveness may serve to drive development of new guidance materials.

Special Focus

One additional area for research that crosses all aspects of the risk assessment continuum is the need to investigate the extent to which carbon nanotubes (CNT) are carcinogenic. While it is known that one type of carbon nanotube, the MWCNTS-7, has been classified by IARC into group 2B-"possibly carcinogenic to humans"-the existing data were not strong enough to generalize all types of CNTs (Grosse et al 2014). Key research needs to reduce gaps in current evidence include: investigation of possible associations between in vitro and early-stage in vivo events that may be predictive of lung cancer or mesothelioma; and systematic analysis of dose-response data across various types of CNTs and the role of physico-chemical properties on precancerous and cancer endpoints (Kuempel et al. 2016). Studies in rodents have shown that certain types of MWCNTs can move to the lining of the lungs where they can potentially cause mesothelioma (Oberdorster et al 2015, Suzui et al 2016). A few recent studies have reported biomonitoring endpoints associated with exposure to MWCNTs, including significantly elevated pro-fibrotic inflammatory mediators (Fatkhutdinova et al. 2016). The concept of high aspect ratio nanoparticles has been in the literature for a number of years and so there is a strong likelihood that some other types of CNTs could be found to be carcinogenic. Therefore, there is a need for further research to clarify this hazard and to describe exposures that occur in different tasks and to assess the risks and management practices that will ensure that workers are protected (Maynard 2016; Schulte et al 2012). There is also a need for research on what extent risks can be managed so as not to significantly increase risks of cancer such as mesothelioma or lung cancer in workers. This risk management research may include studies of controls as well as investigation of ways to design CNTs to be less hazardous (Geraci et al, 2015).

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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