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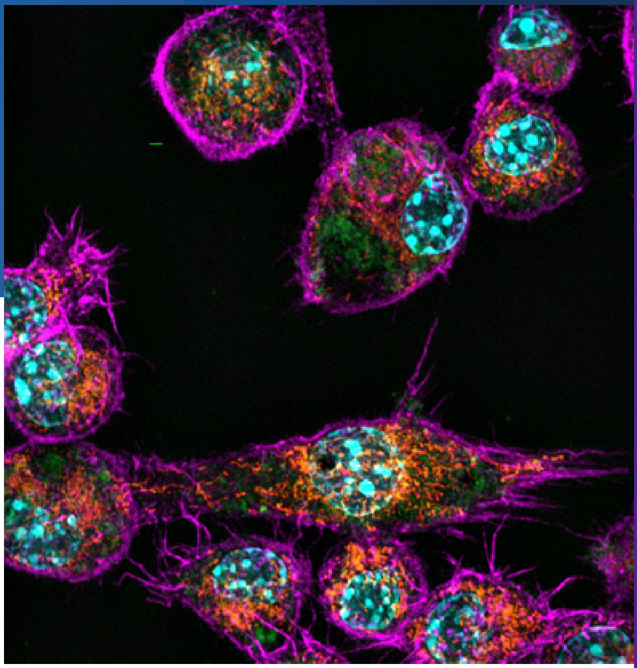

Safe Handling of Engineered Nanomaterials: Turning Knowledge Into Practice

Khara D. Grieger, Christie M. Sayes, Eric Chen,
David S. Ensor, R.K.M. Jayanty

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RTI International
3040 East Cornwallis Road
PO Box 12194
Research Triangle Park, NC
27709-2194 USA

Tel: +1.919.541.6000
E-mail: rtipress@rti.org
Web site: www.rti.org

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About the Authors

Khara D. Grieger, PhD, is currently a risk assessor/environmental research scientist in RTI International's Risk Assessment Program within the Environment, Health, and Safety Division.

Christie M. Sayes, PhD, is a senior scientist with more than 10 years of experience in nanotoxicology, chemistry, and environmental health sciences.

Eric Chen, MS, is a board-certified senior industrial hygienist at RTI International.

David S. Ensor, PhD, is an Emeritus Distinguished Fellow at RTI International.

R.K.M. Jayanty, PhD, ME, is a Senior Fellow and senior program director in the Environmental and Industrial Sciences Division (EISD) at RTI International.

Abstract

Protecting occupational health is one of the most important aspects of achieving the responsible development of engineered nanomaterials (ENMs), especially because workers are often among the first to be potentially exposed to these novel materials. Paul Schulte and colleagues in 2014 were the first to provide specific criteria that organizations may use to help guide responsible nanotechnology development. With these criteria in mind, we evaluate how one research institute has responded to the challenge of handling ENMs in a responsible manner. This effort demonstrates the transition from theory to practice in a workplace setting. Using Schulte et al.'s criteria as a basis, we demonstrate the practical underpinnings of managing ENMs in a workplace setting including the ability to (1) anticipate, identify, and track ENMs in the workplace; (2) assess and communicate hazards and risks to workers; (3) manage occupational health risks; and (4) foster the safe development of nanotechnology and the realization of societal and commercial benefits. In addition, we note remaining challenges pertaining to handling of ENMs and identify four critical research needs to close these information gaps design.

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Introduction

Although there is a general consensus that nanotechnology, including the development of engineered nanomaterials (ENMs), should proceed in a responsible and sustainable manner,[1,2] what this entails has not been clear thus far, particularly for organizations developing and manufacturing ENMs and nano-enabled products. Given this, one recent paper published by authors at the National Institute for Occupational Safety and Health proposed specific criteria for business enterprises and government agencies to follow when developing ENMs and nanotechnology to ensure worker health and safety (text box below).[3] Protecting occupational health and safety is one of the most important aspects of achieving the responsible development of ENMs, especially because workers are often among the first to be potentially exposed to these novel materials. In fact, the nanotechnology industry is expected to employ nearly six million workers in the manufacturing stage of ENM-based products, including 2 million workers in the United States alone,[4-7] and research within the growing field of nanotoxicology has indicated that some ENMs may have the potential to adversely affect human health.[8-11] See Appendix A for definitions of "engineered nanomaterials" and "nanotechnology" and their use in a variety of products and applications.

Criteria to guide occupational health and safety of nanotechnology, as proposed by Schulte et al. (2014)

1. Anticipate, identify, and track potentially hazardous nanomaterials in the workplace
2. Assess workers' exposures to nanomaterials
3. Assess and communicate hazards and risks to workers
4. Manage occupational safety and health risks
5. Foster the safe development of nanotechnology and the realization of societal and commercial benefits

With these model criteria in mind, we document how one multidisciplinary research institute, RTI International, has responded to the challenge of handling ENMs responsibly. We describe the practical underpinnings of developing, handling, and managing ENMs and identify future research needs and opportunities that may help advance the developing field of safe handling of ENMs and ultimately help promote the sustainable development and use of ENMs for all stakeholder groups.

Measuring the Responsible Development of Nanotechnology

How can business enterprises and government agencies measure and verify the responsible development of nanotechnology in practice? Although numerous guidance documents related to occupational safety with respect to ENMs are available,[3,5-7,12] Schulte et al. (2014) were the first to propose specific criteria that could help ensure their responsible development, particularly by nanotechnology business enterprises (e.g., industry, companies), as well as government and regulatory agencies. For business enterprises that manufacture, develop, or handle ENMs, Schulte et al. proposed conducting specific actions across the five general criteria (see Appendix B for the full list). Other actions include identifying ENMs in the workplace, conducting toxicological research, and taking prudent approaches within the criterion "anticipate, identify, and track potentially hazardous ENMs in the workplace."

Measuring how business enterprises implement these proposed criteria and action items is, of course, essential to ensuring the responsible development of nanotechnology with respect to workplace safety and health. At RTI International, several nanotechnology-related research projects have been conducted or are ongoing, including eight listed in Appendix C. These projects range from early phase research and development (i.e., discovery) to full-scale commercial applications (i.e., development). Although not all of these research projects involve the direct handling of ENMs (e.g., the National Institutes of Health [NIH]–funded Nanomaterial Registry, which archives research data on ENMs and their biological/environmental implications), many of them do involve the manufacturing, development, handling, or use of ENMs in various applications. With the Schulte et al. criteria in mind, the following sections describe how RTI International has handled ENMs during these nanotechnology-related projects.

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Anticipate, Identify, and Track Potentially Hazardous ENMs in the Workplace

RTI's workplace safety team fulfills this criterion by anticipating, identifying, and tracking potentially hazardous ENM facilities by its workplace safety team. Through these activities, the identification of ENMs present in the workplace (such as those listed in Appendix C) is performed, including ENMs used in projects focused on conducting toxicological research on diverse ENMs, and RTI takes proactive approaches when handling or dealing with ENMs, such as using diverse risk management measures to avoid or minimize exposures to ENMs in various solid states (Table 1). In addition, internal health and safety teams are also involved in conducting laboratory research and gathering information on the specific ENMs handled or in use, including material identify. Furthermore, RTI has an internal communication system and social media tool (i.e., Salesforce) to enhance communication among staff members in different divisions and research groups. These communication tools can be used to communicate about different nanotechnology-related projects and ongoing activities among researchers so they can continue to anticipate, identify, and track research involving ENMs at RTI.

Assess and Communicate Hazards and Risks to Workers

RTI's health and safety team use standard workplace safety practices to assess and communicate hazard and risk information to workers (Table 1). For laboratory research involving ENMs, health and safety teams conduct hazard and risk assessments to ensure that workers are following safety protocols and regulatory guidelines. In accordance with these practices, the health and safety team communicates hazard and risk information to workers so they understand the rationale for conducting risk management practices such as handling ENMs under ventilation controls and wearing gloves and safety glasses. Workers are also trained to adhere to safe handling techniques, particularly for laboratory researchers and staff who work directly with ENMs

Table 1. Safe Handling of Engineered Nanomaterials (ENMs) at RTI International

	POTENTIAL EXPOSURE ROUTES			
State of ENM	**Inhalation**	**Skin/Eye Contact**	**Ingestion**	**Injection**
Dry powder	• Minimize handling when possible • Handle ENMs under ventilation controls (enclosure, fume hood, glove box) • Wear face mask	**Wear** • Gloves • Safety glasses • Lab coats • Closed-toe shoes	• Use prudent work practices (e.g., no eating or drinking in lab) • Wear face mask	• Dispose of sharps properly with no capping
Suspension (liquid)	• Under most circumstances (non–aerosol-generating activities), inhalation is not a major concern • If aerosol is created, follow standard precautions for dry powder	**Wear** • Gloves • Safety glasses • Lab coats • Closed-toe shoes	• Use prudent work practices (e.g., no eating or drinking in lab) • Replace gloves every 2 hours in lab; remove gloves when exiting lab facilities • Do not use gloves in common areas (e.g., keyboards, facets, door handles	• Use prudent work practices • Conduct needle stick training • Dispose of sharps properly with no capping
ENMs in bulk/ solid material with potential for release	• Keep materials in enclosed spaces • Use ventilation controls	**Wear** • Gloves • Safety glasses • Lab coats	• Use prudent work practices (e.g., no eating or drinking in the lab)	• Dispose of sharps properly with no capping
Manufacturing ENMs	• Isolate the manufacturing process • Use ventilation controls	**Wear** • Gloves • Safety glasses • Lab coats	• Use prudent work practices (e.g., no eating or drinking in the lab)	• Dispose of sharps properly with no capping

in various projects, such as training to handle needle sticks. Finally, Schulte et al. also recommended assessing and measuring workers' exposures to ENMs (Criterion 2). Although RTI assesses potential risks and exposures to ENMs and takes necessary steps to prevent and reduce occupational exposures (see subsequent section for details), measuring an individual staff members' exposures, such as with a personal nanoparticle sampler,[13] is still regarded as a significant hurdle, largely because of the lack of inexpensive, reliable personal monitoring devices specifically for ENMs, as documented by other researchers and organizations.[14-16]

Manage Occupational Safety and Health Risks

RTI conducts a wide range of actions to manage occupational safety and health risks of ENMs, mainly in the form of limiting exposures, based on the state of the ENM (e.g., dry powder vs. liquid suspension) and the potential exposure routes (e.g., inhalation, ingestion, injection) (Table 1). For instance, researchers and staff use personal protection equipment, such as gloves, safety glasses, lab coats, closed-toe shoes, and in some cases, face masks, to reduce the potential for inhalation, skin/eye contact, and ingestion of ENMs in dry powder, suspension, bulk, or solid materials, as well as when manufacturing ENMs. Furthermore, ENMs are handled under ventilation controls, such as enclosures, fume hoods, and glove boxes, or ENMs are manufactured in isolation from other areas to further reduce potential exposures and therefore health and safety risks.

Some practices that workers use to further minimize potential exposures and risks include properly disposing of sharps with no capping, not eating and drinking in labs, not using gloves in common areas (e.g., keyboards, faucets), and replacing gloves every 2 hours. These specific actions minimize potential exposures to workers, researchers, and staff and thereby reduce potential risks of handling and dealing with ENMs. Schulte et al. also recommended monitoring worker exposure and health. Although RTI annually provides the opportunity for free health screenings for all staff at their headquarters, this screening is not geared toward workers and staff handling ENMs.

Foster the Safe Development of Nanotechnology and the Realization of Societal and Commercial Benefits

As a nonprofit research institution whose mission is to improve the human condition by turning knowledge into practice, RTI aims to promote the safe development of nanotechnology in such a way that leads to societal and commercial benefits.* In fact, the nanotechnology projects listed in Appendix C show how these projects range from development applications with clear societal and commercial benefits (i.e., nanofiber-based volatile organic compound sensors, ceramic nanoparticles for next generation dental composites)[18,19] to those that focus on better understanding their potential impacts on health and the environment (i.e., Nanomaterial Registry, toxicity laboratory studies involving C_{60}, risk analysis and decision support).[20,21] In these diverse research projects, discussions of the potential hazards, risks, and uncertainties related to ENMs are integrated naturally, and many of the projects funded by US regulatory agencies such as NIH and the Environmental Protection Agency are designed to support a more proactive approach to developing nanotechnologies and ENMs. Finally, by creating an internal health and safety team dedicated to establishing, monitoring, and conducting workplace safety protocols, RTI can document the effectiveness of various safety controls alongside standard workplace practices.

Future Needs and Opportunities

Although RTI uses a wide range of activities to protect worker health when dealing with ENMs and to foster the development of ENMs in a responsible manner, a number of challenges still exist when working with these novel materials. The development and use of emerging technologies and materials often require the continued evolution of exposure and hazard assessment methods and risk analysis frameworks to ensure that these methods and protocols are well suited for new technologies and materials.[22] Moreover, numerous scientists, researchers, and

* See Grieger et al.[17] for more information on how research institutes like RTI can foster responsible development of nanotechnology through multistakeholder collaborative initiatives.

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government organizations worldwide have proposed various prioritized lists of research needs to ensure workplace safety involving ENMs.[2,7] With these grand-scale research needs in mind, we have identified four critical research needs as particularly important to ensure workplace safety at RTI (text box below).

Critical research needs to ensure workplace safety

- Develop personal exposure monitoring equipment that directly reads worker exposure to ENMs and is inexpensive, reliable, and easy to use
- Develop appropriate exposure and hazard metrics for nanomaterials
- Develop a quantitative structure-activity relationship (QSAR), which aims to understand the relationship(s) between nanomaterial physicochemical properties and cellular responses
- Develop alternative risk assessment or risk analysis approaches specifically for nanomaterials that could be tested on pilot projects

First, inexpensive, reliable, and easy-to-use personal exposure monitoring equipment that directly reads worker exposure to ENMs would significantly enhance the ability to understand real-world exposures under different use conditions. Although several authors and organizations have discussed different techniques that may be applicable to ENMs,[23-26] a practical direct-reading monitoring device for workers would substantially improve ENM monitoring schemes. Second, to understand the implications of ENM exposures to workers, appropriate exposure (and hazard) metrics for ENMs need to be developed, as cited by numerous others.[27,28] Traditional mass-based metrics may not be appropriate for many ENMs, and other metrics, such as particle number and/or surface area, may be better suited. International research teams are working on developing these metrics for a range of ENMs, although it is still undecided which metric(s) may be best for different ENMs or groups of ENMs. Third, developing QSARs would significantly enhance our knowledge of workplace exposure and safety involving ENMs. This predictive tool, which aims to understand the relationship(s) between ENM physicochemical properties and cellular responses, has gained substantial traction in research fields,[10] and further research establishing QSARs for diverse ENMs is clearly needed. Fourth, given the challenges that current risk assessment frameworks face for ENMs,[29] dedicated research is needed to continue developing alternative risk assessment or risk analysis approaches specifically for ENMs. Pilot projects that apply alternative risk analysis frameworks to diverse nanotechnology-related projects, such as those listed in Appendix C, would be a first step to better understanding the potential health (and environmental) risks when dealing with diverse ENMs and would provide an opportunity to further test and develop alternative approaches relevant to ENMs in general.

Conclusions

Although there has been a general consensus that nanotechnology should be developed responsibly to protect worker safety, Schulte et al. were the first to provide tangible, specific criteria that business enterprises and government organizations could use to help guide nanotechnology development. With these criteria in mind, we evaluated how one multidisciplinary research institute (RTI International) has responded to the challenge of handling ENMs. This evaluation shows that although RTI conducts a wide range of activities to protect workers who use ENMs and fosters the responsible development of ENMs, working with these novel materials still poses a number of challenges, as experienced by other research organizations and often cited in the scientific literature.

In response to these challenges, we identified four critical research needs as being particularly important to ensuring workplace safety: development of

1. inexpensive, reliable, and easy-to-use personal exposure monitoring equipment for direct-reading of worker exposure to ENMs;
2. appropriate exposure (and hazard) metrics for ENMs;
3. QSARs to understand the relationship(s) between ENM physicochemical properties and cellular responses; and
4. alternative risk assessment or risk analysis approaches specific for ENMs, using pilot projects based on diverse nanotechnology-related projects.

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Appendix A

Definition and Description of Nanomaterials

Although the term "engineered nanomaterial" (ENM) is still debated within the international scientific community,[30] it is generally defined as a material that is designed and engineered at the nanoscale (approx. 1–100 nm) and is considered to exhibit novel characteristics compared with the same materials at larger scales.[26,31,32] These novel materials are used in a diverse group of products and applications, such as agriculture, automotive, paints and pigments, cosmetics, energy, food products, medical applications, and sensors to name a few.[33] In fact, the National Science Foundation estimates that by the end of the decade the nanotechnology industry will impact $3 trillion on the global economy.[7]

Some of the expected benefits from using ENMs in these applications include stronger, lighter materials; cleaner energy applications; and improved drug delivery. To take advantage of these novel properties, including increased reactiveness, ENMs have already been incorporated into thousands of different products and applications. To date, over 1,600 consumer products on the market contain ENMs as declared by the manufacturer,[34] and it is likely that many more nano-enabled products are available but have not been manufacturer declared. ENMs and nano-enabled products are not just a current reality; they are expected to be vital to emerging and future markets and, thus, are expected to be important to society for decades to come.[1]

Although the numerous potential advantages of developing and using ENMs and nano-enabled products are clear, some concerns have also been raised about their potential to cause adverse and unintended effects on worker health and safety and on the environment. For more than a decade, scientists and researchers have explored the potential for these materials to pose risks to humans and the environment, and although research is still in its early stages, the growing body of literature indicates that at least some ENMs may be problematic under certain exposure scenarios.[33,35-38] These findings are not completely unexpected, considering that many ENMs exhibit different physicochemical properties (e.g., different solubility, electrical conductivity, material strength, magnetic behavior) than the same materials at larger scales,[39] and greater degrees of chemical reactiveness have been known to increase rates of oxidative stress, inflammation, and damage to DNA and proteins.[40] Other concerns have been raised about the diversity of both ENMs and the products that contain them, making testing strategies much more challenging given the diversity of combinations that may be relevant to human and environmental exposures.[36,38] Finally, concerns regarding potential exposures to ENMs also come from previous experiences with chemicals and other emerging risks, in which knowledge of their exposure/toxicity potentials came only after widespread use (e.g., polychlorinated biphenyls, chlorofluorocarbons)[41] or the emergence of new toxicity endpoints (e.g., endocrine disruptors).

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Appendix B

Criteria and Related Actions

The following is a list of criteria and related actions that business enterprises should take to demonstrate the responsible development of nanotechnology, as proposed by Schulte et al.[3]

1. Anticipate, identify, and track potentially hazardous nanomaterials in the workplace.

- Identify engineered nanomaterials (ENMs) in the workplace.
- Conduct toxicological research.
- Take precautionary (prudent) approaches.

2. Assess workers' exposures to nanomaterials.

- Measure exposure.

3. Assess and communicate hazards and risks to workers.

- Conduct hazard and risk assessments.
- Communicate hazard and risk information to workers.
- Train workers in safe handling techniques.

4. Manage occupational safety and health risks.

- Manage workplace risks from ENMs.
- Control exposures.
- Monitor workers exposure and health.

5. Foster the safe development of nanotechnology and the realization of societal and commercial benefits.

- Protect workers from any harm from ENMs.
- Convey the degree of uncertainty known about risks.
- Acknowledge hazards.
- Support precautionary approaches.
- Document the effectiveness of controls

Appendix C

RTI International's Nanotechnology Projects

Researchers at RTI International have been completed or are currently working on the following nanotechnology-related projects.

Nanomaterial Registry. An authoritative, fully curated resource that archives research data on engineered nanomaterials (ENMs) and their biological and environmental implications.[20] Data from the Nanomaterial Registry can be downloaded for individual users. A data quality metric, or compliance score, is applied to characterization data curated in the Nanomaterial Registry. Compliance scores provide an additional level of information to help users in their decision-making processes and are particularly helpful when using secondary data in analyses and models. In addition, the Nanomaterial Registry's Minimal Information about Nanomaterials (MIAN) has been developed with guidance from an advisory board and by leveraging the valuable work done by minimal information working groups. The MIAN contains not only measurement values but also analysis techniques, instruments, protocol and parameter information, and best practices for scientific evaluation. The Nanomaterial Registry is available at: https://www.nanomaterialregistry.org/

Toxicity laboratory studies involving engineered fullerenes (C_{60}). As a part of a National Institutes of Health (NIH)–U19 Center Grant on ENM toxicity led by RTI and involving East Carolina University, in vivo laboratory-based research recently documented that certain types of exposure to engineered fullerenes (C_{60}) resulted in unique cardiovascular consequences that may ultimately lead to increased levels of coronary resistance and myocardial susceptibility to ischemia/reperfusion (I/R) injury.[20] These results were obtained after blood serum showed elevated concentrations of interleukin-6 and monocyte chemotactic protein-1 and coronary arteries showed augmented vasocontraction in response to enthothelin-1 after the addition of indomethacin.

Risk analysis of ENMs and decision support. To form science-based decisions under conditions of uncertainty, structured decision support is needed by a range of decision makers including regulators. Diverse risk analysis projects involving ENMs and subsequent decision support were carried out, including US Environmental Protection Agency (EPA)–funded work to develop a structured decision support framework, including a Web-based version useful for a range of stakeholders; a Department of Defense (DoD)–funded project to identify risky ENMs and associated applications; and RTI-funded projects to understand the implications from potentially new European food-labeling laws related to ENMs.[42]

Nanofiber-based volatile organic compound sensors. Using internal and DoD funding, RTI scientists have invented a sensitive, low-cost, real-time chemical sensor based on polymer fibers filled with carbon nanotubes.[18,19] Potential applications for the sensor include a garment-embedded chemical agent detector for DoD applications and a detector for chlorinated volatile organic compounds (VOCs) in indoor air to better characterize short-term exposure and help identify VOC sources and medical diagnostics.

Ceramic nanoparticles for next-generation dental composites. There has been a major push to eliminate amalgams from clinical use primarily due to environmental disposal concerns. Unfortunately, clinical composite resins do not provide the same mechanical and antimicrobial properties of amalgams, and in many cases they fail prematurely. Therefore, the development of longer-lasting dental resin restorative composites is an urgent public health need. The NIH National Institute of Dental and Craniofacial Research is funding RTI research focused on a better understanding of the interactions of dental resin composites and the surrounding oral environment.

Microbial response laboratory studies involving various ENMs in food and food products. The Food and Drug Administration has expiration date requirements for food supplements and pharmaceutical products. The current approach to determine such dates includes monitoring bacterial growth as one of the critical requirements in a series of tests. Because nanoparticles are an important and fairly new additive in food supplements and several drugs, some scientists wonder whether the existing methods used to determine expiration dates should be revisited. The hypothesis is that including nanoparticles as ingredients affects the expiration date as determined by current methods.

Detection of silver nanoparticles in water for environmental monitoring. This proof-of-concept project involved a working electrode fabricated with a scalable manufacturing approach that could be used to develop a field-portable instrument for environmental monitoring. RTI scientists demonstrated the ability to detect both silver nanoparticles and silver ions in water by electrochemical methods using microfabricated planar electrodes. Using a commercial potentiostat, they showed that the same set of electrodes can be used to detect silver nanoparticles by the nanoparticles' highly characteristic signature, and to detect silver ions by a different electrochemical modality.

Endotoxin concentration of engineered carbon ENMs. RTI scientists reported the first quantification of endotoxin concentrations in commercially provided fullerene, single-wall carbon nanotubes, multiwall carbon nanotubes, and carbon black.[43] The scientists developed a novel sample preparation method using vitamin E surfactant compatible with the *Limulus amebocyte* lysate assay. They found the concentration of endotoxins to be random and not related to material properties such as surface area and surmised the random concentration is likely due to contamination in the material purification and packaging environments. An implication is that endotoxin contamination may be a confounding factor in toxicology studies.

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